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OPINION REVIEW

Hereditary polyposis syndromes remain a challenging disease entity: Old dilemmas and new insights

Frederik Rønne Pachler, Anna Byrjalsen, John Gásdal Karstensen, Anne Marie Jelsig

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Abstract

In this editorial we present an overview and insights of the management of hereditary polyposis syndromes. The primary focus was on familial adenomatous polyposis, juvenile polyposis syndrome and Peutz-Jegher syndrome. Genetic testing has become increasingly available and is easier than ever to integrate into clinical practice. Furthermore, several genes have been added to the expanding list of genes associated with hereditary polyposis syndromes, allowing for precise diagnostics and tailored follow-up. Endoscopic evaluation of patients with hereditary polyposis syndromes is paramount in the surveillance strategies. Current endoscopic procedures include both diagnostic procedures and surveillance as well as therapeutic interventions. Recommendations for endoscopic procedures in the upper and lower gastrointestinal canal were described. Surgery is still a key component in the management of patients with hereditary polyposis syndromes. The increased cancer risk in these patients often render prophylactic procedures or intended curative procedures in the case of cancer development. Surgical interventions in the upper and lower gastrointestinal canal were described with relevant considerations. Development of chemopreventive medications is ongoing. Few drugs have been investigated, including nonsteroidal anti-inflammatory drugs. It has been demonstrated that cyclooxygenase-2 inhibitors may lower the number of polyps. Other medications are currently under investigation, but none have, to date, consistently been able to prevent development of disease.

Key Words: Hereditary polyposis; Familial adenomatous polyposis; Juvenile polyposis syndrome; Peutz-Jegher syndrome

Core Tip: Genetic technologies and testing have evolved immensely over the past decades allowing for tailored surveillance of patients with hereditary polyposis syndromes. These include endoscopic follow-up and surgery when endoscopic management is no longer possible. Chemopreventive drugs may serve as a cornerstone in future management, but it has yet to show consistent prevention of disease progression.

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INTRODUCTION

It is estimated that gastrointestinal (GI) polyps develop in 40%-50% of the population, and risk factors include increasing age, male sex, smoking, and meat consumption[1-4]. The management of one or a few polyps is in many cases straight forward. The polyp is removed, and the histopathology, localization, number, and size guide the need for endoscopic follow-up. However, when multiple or rare types of polyps are detected or when a polyp is detected in young patients, the clinical work-up is less straightforward. In those cases, it may be relevant to consider whether the patient has a hereditary polyposis syndrome. It is important to distinguish polyposis syndromes from spontaneous polyps, as individuals with polyposis syndromes often have a considerable risk of GI cancer. Further, these patients may also have an increased risk of extraintestinal cancer and sometimes other manifestations that may contribute to increased morbidity and mortality[5-7]. Furthermore, first degree relatives may be at risk, as many syndromes are inherited through an autosomal dominant or recessive inheritance pattern.

Clear recommendations for suspecting a polyposis syndrome are difficult to decide upon. The syndromes present with considerable intra- and interfamilial variability, and many patients only have a few polyps and a negative family history. In this paper familial adenomatous polyposis (FAP), juvenile polyposis syndrome (JPS) and Peutz-Jegher syndrome (PJS) were described, as these are the most common.

GENETIC REVOLUTION

Some of the polyposis syndromes have been known for over a century as clinical and hereditary entities (Figure 1). Knowledge of the underlying genetic cause of the syndromes increased when it became possible to investigate variants in the human genome. The first generation of sequencing methods, Sanger sequencing, was developed and commercialized in the 1970s and 1980s. This technique represented a revolution in genetic technology and made it possible to integrate genetic testing in clinical diagnostics[8,9]. Some genes associated with polyposis were discovered in the 1990s and early 2000s, including adenomatous polyposis coli (*APC*) associated with FAP, *mutY* homologue, *STK11*, type IA bone morphogenetic protein receptor (*BMPR1A*) and axis inhibition protein 2 (Figure 1). However, Sanger sequencing is time-consuming and expensive, and it was not until the second (next) generation sequencing methods were developed that further polyposis genes were detected. Next generation sequencing is a form of parallel sequencing that was integrated in clinical practice around 2010. It facilitated fast and cheap sequencing of several genes simultaneously. Thus, genes such as polymerase-epsilon (*POLE*), polymerase delta 1 (*POLD1*), and *NTHL1* have been added as causative of hereditary polyposis[10,11] (Figure 1).

EXPANDING THE PHENOTYPE

The increased knowledge of genetic causes has revealed that several polyposis syndromes have a phenotypic overlap and that at least in the GI tract they mimic each other. Thus, patients with adenomatous polyposis do not always have FAP but may have other rarer syndromes including a polymerase proofreading-associated syndrome where pathogenic variants are detected in the exonuclease domain of *POLE* and *POLD1* or *NTHL1*-related polyposis[12,13]. Concerning hamartomatous polyposis syndrome, JPS is sometimes misdiagnosed because juvenile polyps are mistaken for

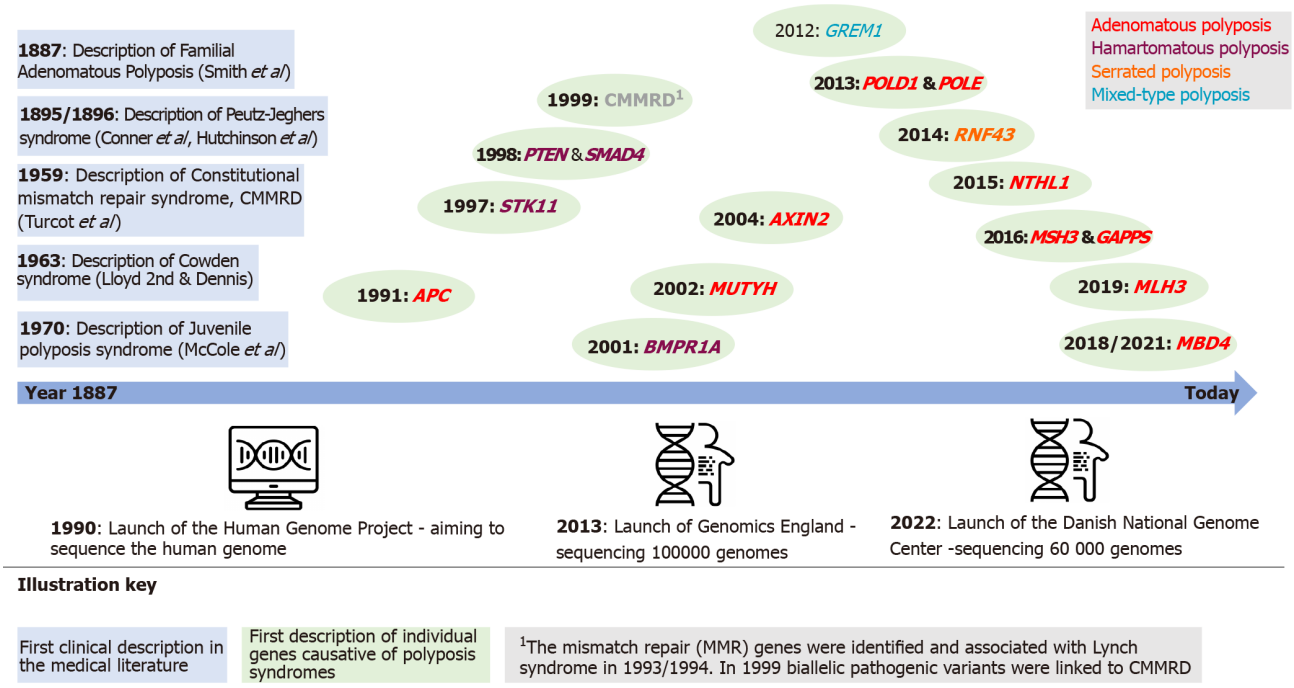

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Figure 1 Timeline of hereditary polyposis syndromes and identification of causative gene. *APC*: Adenomatous polyposis coli; *AXIN2*: Axis inhibition protein 2; *BMPR1A*: Type IA bone morphogenetic protein receptor; CMMRD: Constitutional mismatch repair deficiency; *POLD1*: Polymerase delta 1; *POLE*: Polymerase-epsilon; *MLH*: MutL homolog; *MUTYH*: MutY homologue; *RNF43*: Ring finger 43.

inflammatory polyps[14]. Furthermore, a mixture of polyps with different histopathology sometimes blurs the clinical picture, *e.g.*, in PTEN-hamartoma tumor syndrome (Cowden syndrome, Figure 2) where adenomas and inflammatory, hyperplastic and juvenile polyps can be present[15]. Purely based on clinical manifestations it is often impossible to tell one polyposis syndrome from the other.

It is important to know the genetic subtype, as the risk profile of the patient is different from syndrome to syndrome. The risk of extraintestinal cancer differs with the subtype, *e.g.*, a patient with *NTHL1*-related polyposis has in addition to the risk of colorectal cancer an increased risk of breast and uterine cancer (Table 1). Accordingly, the surveillance strategies should be tailored. Genetic analysis should be integrated in the diagnostic work-up and should comprise a gene panel with polyposis-associated genes as seen in Table 1. Genetic analysis should be carefully interpreted, and if a pathogenic variant is detected, genetic counseling is recommended.

Some efforts have been made to clarify a possible genotype-phenotype correlation especially in the most well-known syndromes like FAP and PJS[16,17]. However, these studies are limited by the small number of patients. Furthermore, the underlying mechanisms that drive cancer development in several of the polyposis syndromes are largely unknown, especially in the hamartomatous polyposis syndromes. A hamartoma-adenoma-carcinoma sequence has been proposed but has yet to be confirmed [18]. It is believed that cancer development in FAP follows the adenoma-carcinoma sequence caused by dysregulation of the Wnt/β-catenin pathway[19]. However, more knowledge on the details of the pathophysiology is necessary to understand the background for polyposis and (extra)intestinal cancer.

SURGICAL MANAGEMENT OF HEREDITARY POLYPOSIS

When a patient is diagnosed or suspected of having a hereditary polyposis syndrome, the primary management include an endoscopic baseline examination with histopathological evaluation of polyps as well as a physical examination with focus on extraintestinal manifestations as seen in the polyposis syndrome[20] (Table 1). There is a phenotypic overlap, as polyposis for most of the syndromes (PJS excluded) is primarily located in the large intestine. *SMAD4*-related JPS and FAP often have polyposis in the upper GI tract (gastric and duodenal polyps, respectively). It is common for all syndromes that when endoscopic management is no longer sufficient then surgical resection is the treatment of choice. Several guidelines have been published on recommended surveillance. However, the evidence level is often low due to a limited number of patients and lack of long-term follow-up studies evaluating different surveillance protocols[20-24].

Table 1 Hereditary polyposis syndromes

Gene (clinical entity)	Inheritance	Cancer risk	Extraintestinal manifestations
Adenomatous polyposis			
APC (familial adenomatous polyposis)	Autosomal dominant	Colon, rectum, thyroid, gastric, hepatoblastoma	Osteomas, dental anomalies, desmoid tumors, epidermoid cysts, CHRPE
AXIN2 (oligodontia-colorectal cancer syndrome)	-	Colon, rectum	Tooth agenesis
POLD1 (polymerase proofreading-associated polyposis)	-	Colon, rectum, uterus, breast, bladder, brain	
POLE (polymerase proofreading-associated polyposis)	-	Colon, rectum, uterus, duodenal, ovary	
MBD4 (*MBD4*-associated neoplasia syndrome)	Autosomal recessive	Colon, rectum, myelodysplastic syndrome, acute myeloid leukemia	
MLH1, MSH2, MSH6, PMS2 (constitutional mismatch repair syndrome)	-	Colon, rectum, hematologic, brain	Café-au-lait spots, neurofibromas
MLH3 (*MLH3*-related polyposis)	-	Uncertain; potentially colon, rectum, gastric, brain, breast	
MSH3 (*MSH3*-related polyposis)	-	Uncertain; potentially colon, rectum, gastric, brain, breast	
MUTYH (*MUTYH*-associated polyposis)	-	Colon, rectum, ovary, bladder, breast, uterus, gastric, pancreas, skin	
NTHL1 (*NTHL1* tumor syndrome)	-	Colon, rectum, breast, duodenum, uterus	
Hamartomatous polyposis			
BMPR1A (juvenile polyposis syndrome)	Autosomal dominant	Colon, rectum	
PTEN (*PTEN* hamartoma tumor syndrome)	-	Colon, rectum, thyroid, breast, kidney, uterus	Macrocephaly, trichilemmomas, autism, hemangiomas, arteriovenous malformations
SMAD4 (juvenile polyposis syndrome)	-	Colon, rectum, gastric	HHT, thoracic aneurysm
STK11 (Peutz-Jeghers syndrome)	-	Colon, rectum, duodenum, breast, ovary, pancreas, gastric, cervical	Mucocutaneous pigmentation
Serrated polyposis			
RNF43 (serrated polyposis syndrome)[1]	Autosomal dominant	Colon, rectum	
Mixed-type polyposis			
GREM1 (hereditary mixed polyposis syndrome)	Autosomal dominant	Colon, rectum	

[1]Ring finger 43 only accounts for a fraction of serrated polyposis syndromes.

APC: Adenomatous polyposis coli; *AXIN2*: Axis inhibition protein 2; *BMPR1A*: Type IA bone morphogenetic protein receptor; CHRPE: Multifocal/bilateral congenital hypertrophy of the retinal pigment epithelium; HHT: Hereditary hemorrhagic telangiectasia; *MLH*: MutL homolog; *MSH*: MutS homolog; *MUTYH*: MutY homologue; *POLD1*: Polymerase delta 1; *POLE*: Polymerase-epsilon; RNF43: Ring finger 43.

LOWER GI ENDOSCOPY AND SURGERY

Virtually all patients with polyposis syndromes undergo colonoscopy surveillance. The appropriate intervals and recommended age to initiate surveillance are debated. It is widely recommended that individuals with FAP are examined annually or biannually from the early teenage years[20,24]. Development of cancer in patients with FAP is extremely rare before the age of 15[20,24-26], and it could be argued that endoscopic examinations should not start earlier than this.

During colonoscopy investigation, the use of chromoendoscopy, either direct or virtual with narrow band imaging, is often used. Narrow band imaging has not been shown to increase detection of neoplastic polyps, but it is a helpful tool in skilled hands[27]. In patients with FAP a prophylactic colectomy is often indicated as most FAP patients will develop adenomatous lesions (Figure 2), and endoscopic surveillance is insufficient[20,24,26]. However, it is now clear that patients who have a pathogenic variant in *APC* have a very variable phenotype. Some may develop polyps at a later age, and thus family history should always be considered when recommending surveillance and deciding on surgery. Subtotal colectomy with ileorectal anastomosis (IRA) or proctocolectomy, often with the intent

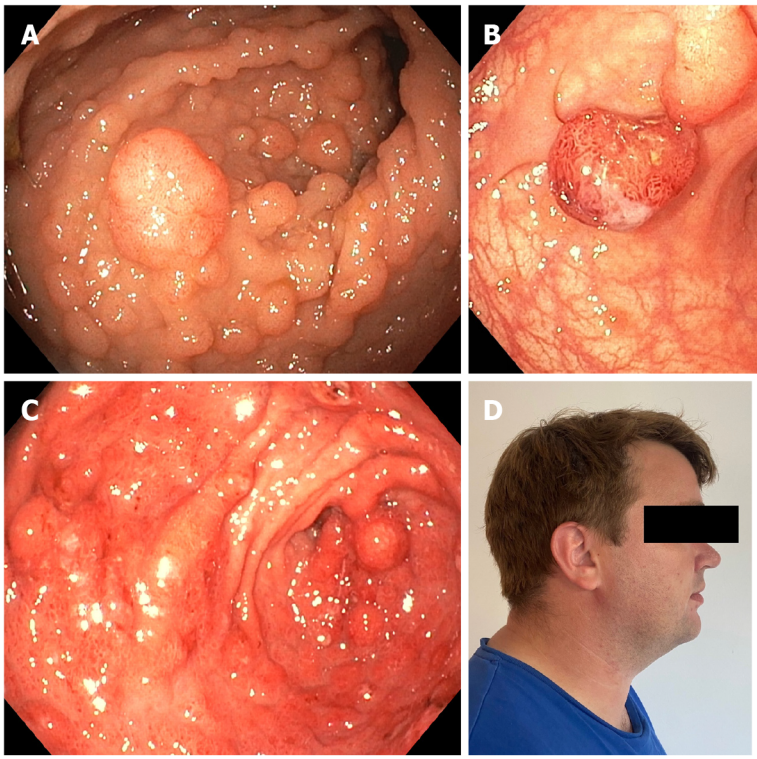

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Figure 2 Polyps and extraintestinal manifestations in patients with hereditary polyposis syndromes. A: Severe colonic adenomatosis in a patient with familial adenomatous polyposis; B: Colonic polyposis in patient with Peutz-Jegher syndrome; C: Severe gastric polyposis in patient with SMAD4-related juvenile polyposis syndrome; D: Patient with Cowden syndrome and macrocephaly.

of restorative proctocolectomy with ileal-pouch anal anastomosis (IPAA), are recommended for patients with FAP[20,23,24,26,28]. Surgery for patients who are known to have FAP from childhood often occur in their late teenage years but may be sooner or later if endoscopic findings dictate it. Surgery before the age of 15 years is not recommended[20,23,24,26,28].

After colectomy endoscopic surveillance annually or biannually is recommended[20,24]. However, it is heavily debated whether patients with IRA and patients with restorative proctocolectomy with IPAA should follow the same intervals. If polyposis progresses during surveillance in patients with IRA, proctectomy, possibly with IPAA, should be considered. This may be the appropriate choice, especially in patients with FAP, in the presence of numerous rectal polyps since excessive resection may lead to functional problems and technical difficulty in future proctectomy[20-22,28,29].

In all cases of colectomy, proctocolectomy with terminal ileostomy is also an appropriate solution. However, most patients undergoing resection are relatively young, and a permanent stoma may impact their quality of life[30]. Hence, it is often desirable to attempt anastomosis with preserved continence, but this should be a subject for discussion and individualization.

In patients with JPS and PJS the initial colonoscopy is usually recommended around the age of 12 years for JPS[20,22,31] and 8-10 years for PJS[22,29,31] and repeated every 2-3 years, although recommendations differ. Patients with JPS or PJS should be offered colectomy, either segmental or subtotal with IRA or restorative proctocolectomy with IPAA if the colorectal polyp burden is too high for endoscopic management or if cancer develops[21,22,29]. A further indication for resection in this population may be severe bleeding from colonic neoplasia[21,22,29] (Figure 2).

UPPER GI ENDOSCOPY AND SURGERY

For some polyposis syndromes, upper GI surveillance is recommended due to a high risk of polyposis and/or cancer. In patients with a pathogenic variant in *APC* associated with FAP, esophagogastroduodenoscopy (EGD) is recommended from 25 years of age. It may be initiated earlier if colonic polyposis is present in the teenage years[20,24]. In recent years, it has become more frequent to perform EGD with a cap-assisted forward viewing endoscope, which has been shown to be safe and visualize the papilla in most patients[32].

It is widely recommended to alter surveillance according to the Spigelman staging of polyps[33,34]. Depending on the EGD findings and histopathological evaluation, total duodenectomy may be relevant in patients with FAP. As a guidance to the timing of duodenectomy, the Spigelman classification may

used[20,24]. Duodenectomy is recommended in patients with stage IV or evidence of cancer[20,24].

In some cases, it is recommended to perform a pancreas preserving total duodenectomy, which facilitates an easier endoscopic surveillance compared to post-Whipple procedure. It is proposed that EGD screening in patients with JPS should start in the early teenage years and be repeated every 2-3 years[20,22]. Several upper GI resections may be relevant in patients with JPS, especially those who have a pathogenic variant in *SMAD4* since they have a higher risk of gastric polyposis and gastric cancer compared to JPS and pathogenic variants in *BMPR1A*[14]. In the case of development of numerous and/or very large gastric polyps, partial or total gastrectomy is advised[21,22,29].

In patients with PJS, initial EGD is recommended at the same time as the initial colonoscopy, usually at age 8-10[20-22,29]. The repeat interval should be based on endoscopic findings, but due to the increasing risk of polyposis with age, the interval should at minimum be every 2-3 years[20-22,29] (Figure 2). Upper GI resections in patients with PJS should in general be segmental, although indications should be made with some restraint[21,22,29]. It is recommended to perform the smallest possible, oncologically safe resection to prevent the risk of short bowel syndrome. Indications include suspicious lesions, repeated symptomatic bleeding and obstruction or intussusception caused by polyps[21,22,29]. Small bowel resection in patients with JPS follow the same recommendations. It is advised to perform intraoperative enteroscopy when performing small bowel resections to evaluate the extent of polyposis.

OTHER ENDOSCOPIC PROCEDURES

In PJS, polyps mainly develop in the in the small bowel, and invagination is a frequent first symptom [21,22,29]. It is usually recommended that patients with PJS undergo a baseline video capsule endoscopy at the beginning of endoscopic screening[21,22,29]. Intervals for video capsule endoscopy should depend on the endoscopic findings.

CONCLUSION

As more and more families are identified and genetic testing is becoming more sophisticated, research into preventing symptomatic disease has increased. In patients with FAP, the primary focus has been on nonsteroidal anti-inflammatory drugs, which have been shown to decrease the number of adenomas. Two agents in particular have been studied: Sulindac and celecoxib. Both have demonstrated a decrease in the amount of colorectal adenomas, but celecoxib also decreases the number of duodenal adenomas [28]. Treatment with nonsteroidal anti-inflammatory drugs inherently has a risk of GI complications, most of which can be managed with protein-protein interaction. Celecoxib, a selective cyclooxygenase-2 inhibitor, has the disadvantage of an increased risk of cardiovascular side effects. Treatment with celecoxib has shown similar results in patients with PJS. Polyps in PJS overexpress cyclooxygenase-2, and the decrease in polyp burden is thought to be due to inhibition of this expression[20]. In addition, some older studies have shown that rapamycin (sirolimus) affects the polyp burden and size in mouse models[35,36]. Further therapeutics are under ongoing investigation and aim to target the involved pathway. In JPS, both *BMPR1A* and *SMAD4* encode proteins working in the transforming growth factor-beta pathway, and as it is also frequently involved in sporadic cancer several attempts have been made to target this[37]. Recommendations as to which patients should use chemoprevention differs, but since no agents have been shown to prevent development of disease, the endoscopic and surgical measures, as described above, should be the primary focus.

FOOTNOTES

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MINIREVIEWS

Application of ablative therapy for intrahepatic recurrent hepatocellular carcinoma following hepatectomy

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Abstract

The post-hepatectomy recurrence rate of hepatocellular carcinoma (HCC) is persistently high, affecting the prognosis of patients. An effective therapeutic option is crucial for achieving long-term survival in patients with postoperative recurrences. Local ablative therapy has been established as a treatment option for resectable and unresectable HCCs, and it is also a feasible approach for recurrent HCC (RHCC) due to less trauma, shorter operation times, fewer complications, and faster recovery. This review focused on ablation techniques, description of potential candidates, and therapeutic and prognostic implications of ablation for guiding its application in treating intrahepatic RHCC.

Key Words: Hepatocellular carcinoma; Recurrence; Ablation techniques; Radiofrequency ablation; Combined therapy; Therapeutic index

Core Tip: The high recurrence rate of hepatocellular carcinoma (HCC) remains a global health challenge, which urges close surveillance following hepatectomy for earlier detection of recurrent HCC. Unlike primary HCC, recurrent HCCs are usually detected in the early stage but are not amenable to repeat hepatectomy after comprehensive evaluation. The value of ablation as a minimally invasive but curative method is an increasing concern. We herein discuss the role of various ablation modalities and procedures in treating intrahepatic recurrent HCC for guiding its better application.

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INTRODUCTION

Hepatocellular carcinoma (HCC), with high morbidity, mortality, and recurrence rates, remains a global health challenge[1]. Surgical resection is considered the main strategy for long-term survival of patients with HCC. However, the incidence of recurrence reaches approximately 70% 5 years after hepatectomy, even in patients with a single tumor ≤ 2 cm[2]. Advances in preoperative prediction and postoperative follow-up strategies have facilitated the earlier detection of recurrent HCC (RHCC)[3-5], allowing for more treatment options. Thus, an appropriate therapeutic option is crucial for achieving long-term survival of patients with recurrence after surgery, which requires a comprehensive understanding of possible treatments and thorough evaluation of the patient.

With the necessity to fully consider the initial treatment, the clinicopathologic characteristics of primary HCC, recurrence interval, the characteristics of RHCC, general condition of the patient's liver, and other factors[6,7], treating RHCC cannot exactly follow the guidelines for primary HCC. Considering that inadequacy of residual liver volume, postoperative liver decompensation, intra-abdominal adhesions and anatomical variation following initial resection increase difficulty and risk of re-resection, only about 19% of well-selected patients can receive secondary surgery for a definite survival benefit in clinical practice[8,9]. Ablation as a curative but less invasive treatment may be considered in the management of RHCC.

Local ablative therapy has been established as a treatment option for resectable and unresectable HCCs according to current clinical guidelines[3,10], which can provide a sustained complete response, a lower complication rate, and a 5-year survival rate of 68.5% for early HCC, even initially operable HCC [11]. The extensive and promising application of ablation in primary HCC makes it a feasible approach for the treatment of intrahepatic RHCC. This review demonstrated the role of ablation in treating RHCC, focusing on different ablative techniques, descriptions of potential candidates, as well, therapeutic and prognostic implications for guiding its better application.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is the most commonly used modality for treating both primary and recurrent HCC. Meanwhile, RFA has gained an increasing role owing to its efficacy and safety. When the electrode tip is inserted into the selected tissue to generate electric current, RFA induces ionic agitation, local heat, and subsequent coagulation necrosis[12]. Some factors, such as centrifugal heat propagation, “heat-sink effect” mediated by blood perfusion, and increased impedance due to tissue charring limit the size of the ablation zone and reduce the efficacy[13]. These also have driven continuous device and procedure improvements: Multi-tined expandable electrodes, internally cooled electrodes, multipolar ablation using bipolar electrodes, and simultaneous vessel obstruction[13-15].

Candidates

For intrahepatic recurrent HCC after hepatectomy, the indications for RFA[16-18] are as follows: Within the Milan criteria at recurrence, satisfying a single lesion (≤ 5 cm in diameter) or three or fewer lesions (each ≤ 3 cm in diameter) without macrovascular invasion or distant metastasis; Child-Pugh grade A or B liver function; Eastern Cooperative Oncology Group performance score of 0 to 1; no uncorrectable coagulation status; no severe varices and intractable ascites; and an acceptable and safe path evaluated by imaging.

Therapeutic and prognostic implications

Bai *et al*[18] analyzed the long-term survival of solitary RHCC of 5 cm or less after RFA, and the rates of primary technical success, local tumor progression (LTP), and 1-, 3-, 5-, and 10-year overall survival (OS) post ablation were 94.8%, 11.2%, 94.0%, 71.8%, 54.5%, and 33.7%, respectively, in the RHCC following hepatectomy subgroup, which was similar to primary HCC of 5 cm or less after RFA. The safety and efficacy of RFA for RHCC are being gradually affirmed by clinical studies, and an increasing number of retrospective studies comparing repeat hepatectomy and RFA, especially for early stage RHCC, have been reported in recent years. The comparison outcomes of survival between the two groups are conflicting, with inherent selection biases, either equivocal or favorable for one. The majority reported that RFA provided similar OS to repeat hepatectomy for RHCC, with 5-year OS rates of 26%-71%, but

with fewer major complications (0%-1.6% *vs* 2.6%-9.1%) and shorter hospital stays (3-5 d *vs* 8-14 d)[19-25].

Xia *et al*[17] conducted a randomized clinical trial for comparing long-term survival results following repeat hepatectomy with those following percutaneous RFA in 240 patients with early stage RHCC. They found no significant difference in the 1-, 3-, and 5-year OS rates between the two groups (92.5%, 65.8%, and 43.6% *vs* 87.5%, 52.5%, and 38.5%, respectively). However, RFA was linked to a greater risk of local repeat recurrence and early repeat recurrence than repeat hepatectomy, consistent with the findings of a retrospective multicenter study[25] which concluded that repeat hepatectomy for RHCC within the Milan criteria resulted in longer recurrence-free survival and less frequent early repeat recurrence (less than 12 mo). The rate of inaccurate ablation and the possibility of the presence of satellite nodules increase as the target size of RFA increases in general, leading to an inferior to repeat hepatectomy for local tumor control and a tendency toward a shorter recurrence-free survival of RFA.

A number of factors reported previously were associated with worse survival of RHCC following treatment, including larger and multiple resected tumors, the presence of microvascular invasion (MVI) at initial hepatectomy stage, time to recurrence (TTR) ≤ 1 year, poor Child-Pugh class, portal hypertension, serum-fetoprotein (AFP) level greater than 200 ng/mL, larger and multiple RHCC at recurrent stage, *etc*[18,21-26]. These factors resulted in a higher tumor burden, poorer liver function, and more aggressive behavior, which needed to be considered for appropriate therapeutic strategies.

Xia *et al*[17] found that percutaneous RFA ablation was related to worse local tumor control and OS than repeat hepatectomy in patients with target diameter > 3 cm or AFP level > 200 ng/mL. Small ablated tumors (≤ 3 cm) can achieve higher complete response rates of > 95%[16,26,27]. For larger tumors (> 3 cm), an overlapping ablation strategy, other ablation modalities, or combination of transarterial chemoembolization (TACE) and RFA were required to produce ablation zones more reliably and sufficiently[28].

A previous study[29] focused on RHCC with MVI-positivity at initial hepatectomy and concluded that repeat surgery/RFA can provide a better survival outcome for selected BCLC stage 0-A patients than TACE, which was contrary to the results of Meniconi *et al*[6] and Jin *et al*[30] They concluded that TACE seemed more appropriate than curative treatments in a small sample of early stage MVI-positive HCC. Early recurrence (TTR ≤ 1 or 2 years) is generally related to intrahepatic metastases, MVI, and microsatellite lesions generated by primary HCC, with poor survival after hepatectomy[31]. Yang *et al*[32] reported that patients with late recurrence (> 1 year) had better survival outcomes after RFA than those with early recurrence (≤ 1 year). The comparison between repeat hepatectomy and RFA for RHCC with different TTR was conducted in a limited number of studies. Liang *et al*[19] and Xia *et al*[17] found that the OS was similar between the two treatments in patients with a TTR ≤ 1 year or > 1 year. Lu *et al*[33] showed that the post-recurrence survival rates for the repeat hepatectomy group were better than those for the RFA group of patients with early recurrence (TTR ≤ 2 years). However, no significant difference was found in the late recurrence group (TTR > 2 years). Sequential TACE and RFA were found to offer a better OS for patients with recurrence ≤ 1 year than RFA alone, but not for those with recurrence for more than 1 year[28]. With the different results of limited studies, treatments for these particular populations will be required further investigation.

Complications

The morbidity and mortality of RFA are obviously lower than those observed following repeat hepatectomy for RHCC, while the rate of complications increases when performing more aggressive procedures for larger tumors and targets at-risk location or at poor liver and general condition. Pain and fever post-ablation are common but remain short after symptomatic treatment. The major complications of RFA include pneumonia, pneumothorax, pleural effusion, hemoperitoneum, ascites, liver hematoma, liver abscess, subdiaphragmatic abscess, liver failure, injury or perforation of adjacent structures such as diaphragm, gallbladder, colon or stomach, ileus, wound or puncture site infection and tumor seeding [17,18,25]. A reasonable RFA protocol for well-selected patients is crucial for protecting surrounding tissues and preventing complications.

OTHER AVAILABLE ABLATIVE TECHNIQUES

Microwave ablation

Microwave ablation (MWA), an emerging alternative modality to RFA, causes thermal coagulation by utilizing microwaves at a frequency of 2450 MHz to induce the vibration and rotation of water molecules within the tissue and subsequent heat generation[34]. MWA have theoretical advantages over RFA including a higher temperature, a faster heating of a larger target, a less "heat-sink effect" and insensitivity to tissue conductance[13]. The first-generation MWA was initially limited by technical problems related to sub-optimal power handling, large antenna diameter and antenna shaft heating. Its resulting ablation zone is small and more elliptic[35,36]. Thus new-generation MWA have developed and simultaneous power delivery technique of multiple antennas has been tried for producing reliable and large spherical ablation zone[37,38]. Zhang *et al*[39] evaluated the efficacy of US-guided

percutaneous MWA for RHCC measuring ≤ 5 cm and get 5- and 7-year OS rates of 39.6% and 17.3%, respectively. Ryu *et al*[40] performed MWA during open surgery in 75 patients with intrahepatic recurrence after hepatectomy and identified MWA as a safe and feasible procedure, which provided a 5-year survival rate of 55.4%, comparable to results reported previously for re-resection, RFA, and MWA for primary HCC. The application of MWA in RHCC was slowly being recognized, and more data will be needed to demonstrate its value for larger RHCC and its efficacy over RFA.

Percutaneous ethanol injection

Ethanol injected into the tissue induces coagulation necrosis mainly because of its dehydronative and protein degenerative effects and partly because of its thromboembolic effect[41]. Percutaneous ethanol injection (PEI) could be precisely applied to ablate HCC ≤ 2 cm in diameter, but the necrosis rate is reduced and the local recurrence rate increases for larger tumors[42]. Compared to thermal ablation, it is inexpensive and has a low rate of adverse effects even for patients with Child-Pugh class C or tumors at risk locations; however, repeated injections are often required for effective treatment. These characteristics have promoted its application in combination therapies[43]. Yin *et al*[27] treated 288 patients with post-hepatectomy RHCC (maximum diameter ≤ 7 cm and number ≤ 5) using PEI, RFA, MWA, or PEI combined with RFA. The incidence of LTP in the PEI group was 19.5% and no significant difference was found among the four ablative modalities. However, selection bias existed, and the authors did not focus on comparing the efficiencies of the different techniques.

High-intensity focused ultrasound ablation

High-intensity focused ultrasound ablation (HIFU) ablation is an extracorporeal conformal therapy that can achieve heat-induced coagulation necrosis without the need for surgical exposure or probe insertion. Heat generation is mediated by focusing high-intensity ultrasound beams on the target using the extracorporeal motion of a multi-element ultrasound transducer. HIFU, which is noninvasive and conformal, can ablate a large volume of tumor with no worry of tumor seeding along the needle tract [44]. The value of HIFU or HIFU combined with TACE in unresectable HCC has been previously reported[44,45]. A study[46] showed that HIFU was a safe and feasible treatment modality for RHCC with an acceptably low morbidity rate and a comparable survival outcome to RFA, which was conducted among a small number of patients meeting the Milan criteria. HIFU have not get widespread adoption yet, probably as ultrasound propagation influenced by different tissues, ultrasound artifacts and respiration motion add time consumption and technical challenge relative to other ablation modalities[47]. There is no additional clinical data with HIFU for RHCC currently.

Cryoablation

Cryoablation (CRA) is a thermal technique that uses cryoprobes to transfer low temperatures caused by the Joule-Thomson effect with super-cooled gas or liquid expansion, and achieves tissue necrosis by alternating cycles of freezing and thawing, which induces denaturation of cellular proteins, cell membrane rupture, cell dehydration, and ischemic hypoxia[48]. Cryoshock, a severe adverse event associated with multiorgan failure post-CRA, has been reported in previous studies, but the new generation of cryoablation systems with ultrathin cryoprobes that use argon-helium may lead to a low risk of bleeding and cryoshock[49]. The main advantage of CRA over heat-based ablation modalities is a well-visualized ice ball on ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) during ablation for precise monitoring, which contributes to the potential value of cryoablation for targets larger or close to important structures[48]. A multicenter randomized controlled trial showed a significantly lower LTP after CRA than after RFA for HCCs sized 3.1-4.0 cm[50]. For RHCC, Chen *et al* [51] used percutaneous CRA to treat 76 tumors (≤ 7 cm) in 26 recurrent patients and confirmed its efficacy with 1- and 3-year OS rates of 70.2% and 28.8%, respectively; however, further research is insufficient.

Irreversible electroporation

Irreversible electroporation (IRE) works by short pulses of high intensity delivered between two electrodes (convergent centripetal technique), which produce irreversible pores in the cellular bilayer membrane for cell death, while the connective tissue, blood vessels, and bile ducts are preserved. It is a nonthermal ablative method with no influence of the "heat-sink effect", a lower risk of thermal injury, and less frequent liver failure[13]. Therefore, it can be considered for the treatment of dangerous sites and poor liver function[52]. This procedure can only be performed in patients with normal cardiac rhythm, because high-intensity pulses can cause myoclonia and severe arrhythmias. Overall, IRE could be indicated for a wider range of candidates than thermal techniques with consideration of patient condition, cost, and operational complexity, although more clinical data are required to validate its efficacy.

Various ablation modalities have their advantages and limitations (Table 1). RFA has been confirmed to be effective and used for RHCC with an increasing frequency; however, available data on other ablation modalities are insufficient, and limited studies have sought to directly compare the effects of various ablation techniques for treating RHCC.

Table 1 Description characteristics of different ablation modalities

Ablation modalities	Advantages	Limitations
RFA[13,14]	Most widely used and mature technology	Limited zone of monopolar centrifugal ablation
	Multibipolar RFA for larger and more modulable ablation zones	Sensitive to heat sink effect
		Influenced by tissue conductance
MWA[13,14]	Higher temperature and faster heating of larger target over RFA	Complex and technically demanding operation
	Less sensitive to heat sink effect	Thermal injury from higher temperature
	Less influenced by tissue conductance	
PEI[42]	Simple to perform, inexpensive	Small size of ablation zone
	Chemo-ablation: No thermal injury	High local recurrence rate
HIFU[47]	Noninvasive operation: No worry of needle tract seeding	Time consuming
		Influenced by ultrasoundpropagation and artifacts, respiration motion
CRA[13,48]	Less pain	High cost
	Well-visualized ice ball on imaging for precise monitoring	Cryoshock (more often in early device)
IRE[13,14]	Nonthermal ablation: low risk of thermal injury	Risk of myoclonia and arrhythmias
	Less sensitive to heat-sink effect	Limited clinical data
	Well preserved connective tissue, blood vessels and bile ducts	
	Less frequent liver failure	

RFA: Radiofrequency ablation; MWA: Microwave ablation; PEI: Percutaneous ethanol injection; HIFU: High-intensity focused ultrasound ablation; CRA: Cryoablation; IRE: Irreversible electroporation.

ABLATION IN COMBINED THERAPY

Various combinations of treatments have been explored to improve the local tumor control and survival outcomes of ablation. The available experience with ablation combination therapy for RHCC has mainly focused on RFA.

RFA and PEI

Ethanol injection can reduce the "heat-sink effect" by destroying vessels within or around the tumors and promoting thermal conduction by lowering the extent of carbonization of the tissue. Therefore, RFA started after PEI completion could induce an enlarged ablation zone with an adequate safety margin compared with RFA alone, improving local control and reducing distant recurrence[53,54]. Chen *et al* [43] retrospectively compared the efficacy and safety of RFA and PEI (RFA-PEI) with repeat hepatectomy in elderly patients (≥ 70 years) with RHCC within the Milan criteria after initial surgery. The 1-, 3-, and 5-year OS and RFS rates after RFA-PEI were 78.2%, 40.8%, and 36.7%, and 69.5%, 37.8%, and 33.1%, respectively, comparable to those of repeat hepatectomy. They confirmed the good efficacy and high safety of RFA-PEI for RHCC, even for patients with poor performance status who urgently require minimally invasive treatments.

RFA and TACE

Because occlusion of blood flow by TACE before RFA reduces the "heat-sink effect" and the hyperthermia of RFA enhances the effect of anticancer agents on cancer cells, the sequential combination of TACE and RFA can extend the ablation zone and promote the ability of TACE to completely destroy the whole lesion. Peng *et al*[55] reported TACE-RFA provides comparable OS and disease-free survival (DFS) to repeat hepatectomy, fewer major complications and shorter hospital stay. Yang *et al*[56] demonstrated that the 5-year survival of patients with RHCC after hepatectomy was significantly higher in the combination group than in the TACE or RFA group, but there was no significant difference in survival among these three groups with < 3 cm RHCC, consistent with the conclusion of a prospective randomized trial[28]. They further confirmed the benefit of the sequential combination treatment for RHCC measuring 3.1-5.0 cm but not for those with tumors 3 cm or smaller and also recommended it for

patients with tumors that recurred 1 year or less, which can be explained by the increased chance of clearance of micrometastases in combination treatment.

RFA and systemic treatment

The combination with systemic therapy has been considered effective to impede rapid progression of residual tumors due to inadequate RFA and control advanced HCC[57]. Peng *et al*[58] investigated the role of Sorafenib combined with TACE-RFA in the treatment of advanced RHCC after initial hepatectomy and proved its safety, efficacy and superior survival outcomes over sorafenib alone. These benefits might be due to Sorafenib suppressing angiogenesis induced by TACE or inadequate RFA. The combination of RFA and immunotherapy is also considered rationale. Ablation boosts the T cell immune response to improve the efficacy of immunotherapy and immune checkpoint inhibitors block immune escape to reduce recurrence after ablation[59]. A retrospective study[60] reported that patients with RHCC had significantly better RFS and OS outcomes in the RFA plus anti-PD-1 group than in the RFA alone group. However, additional trials are required to confirm these interesting findings.

TECHNICAL IMPROVEMENTS FOR EXTENDING THE APPLICATION OF ABLATION

Ablation procedures can be performed percutaneously, laparoscopically, or at open surgery, using various imaging guidance techniques, including US, CT, or MRI. In general, ablation is appropriate for treating lesions within the Milan criteria and distant from the adjacent organs. In addition to the above-mentioned ablation modalities and combination treatments, multiple options of performing paths, guidance strategies, and other technical advances may allow extensive access to curative ablation therapy, especially for patients with a poor profile and tumors with large size, invisibility on US, or risk location.

Laparoscopy and laparotomy over percutaneous RFA provide greater exposure and more direct observation of the tumor and surrounding structures and can be used to temporarily occlude blood flow to increase the ablation zone. Santambrogio *et al*[61] performed laparoscopic thermal ablation for the treatment of intrahepatic RHCCs (within Milan criteria) that required repeated punctures or adjacent to visceral structures. Laparoscopic ablation was proposed as a safe and effective treatment for RHCC, leading to survival and DFS rates similar to those of primary HCC patients undergoing laparoscopic ablation without increasing morbidity. Contrast-enhanced US, CT, MRI, and image fusion can better delineate the target and final extent of the ablation zone, remedying the limitation of lesion invisibility in conventional US. Song *et al*[62] and Zhao *et al*[63] performed US-CT/MRI fusion–guided RFA for recurrent HCC that was subcentimeter or invisible on US, and both achieved technical success and efficacy rates of over 94%. Lin *et al*[64] conducted MWA guided by enhanced liver-specific MRI in 18 patients with small RHCC and achieved 100% technical success rate.

Furthermore, the creation of artificial ascites or artificial pleural effusion, balloon catheter interposition, three-dimensional visualization technology, fluoroscopic real-time guidance, and other assistive techniques are all effective in ablation safety, a high rate of success, and expansion of indications for ablation[65-68].

CONCLUSION

The role of ablation in intrahepatic RHCC was shown in Figure 1. Unlike primary HCC, RHCCs are usually detected in the early stage but are not amenable to repeat hepatectomy with consideration of inadequate liver remnants, limited liver function reserves, and technical difficulties due to adhesions following initial surgery. The value of ablation as a minimally invasive but curative method is an increasing concern. For patients who are eligible for ablation and repeat hepatectomy, clinicians need to balance the worse local control and lower major complication rates or shorter hospital stays when making ablation decisions. Various ablation modalities and procedures are continuously improving, and combination strategies may add additional benefits, which promote the extended application of ablative therapy. Further exploration of a particular population with risk prognostic factors and sufficient experience on the efficacy of different ablation modalities and techniques in treating RHCC are required and based on randomized clinical trials with larger sample sizes. Moreover, evidence that ablation could boost the immune response raises expectations for its combination with immunotherapy for advanced RHCC.

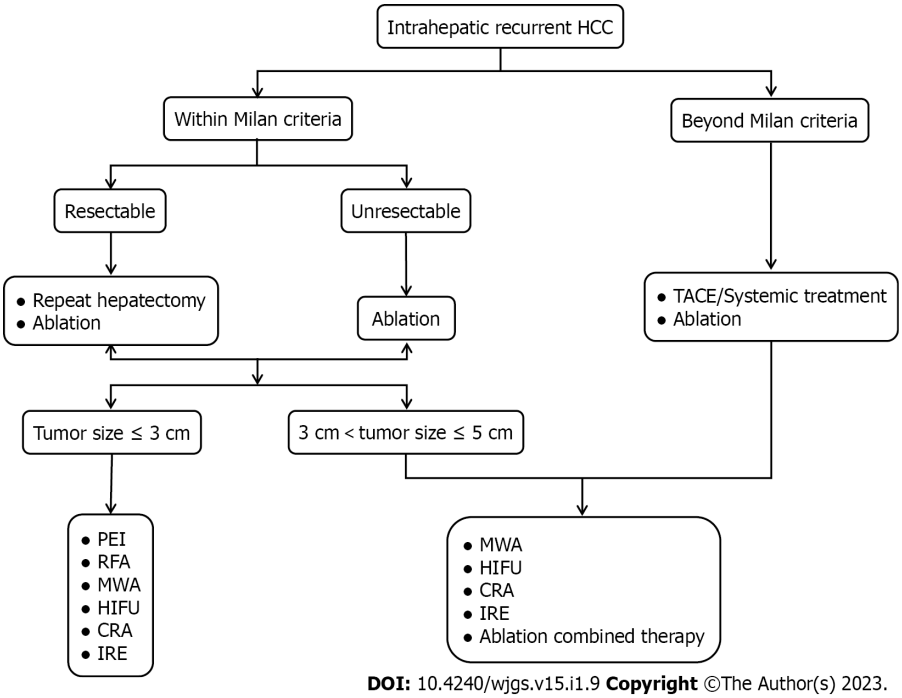

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Figure 1 Role of ablation in intrahepatic recurrent hepatocellular carcinoma. HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; MWA: Microwave ablation; PEI: Percutaneous ethanol injection; HIFU: High-intensity focused ultrasound ablation; CRA: Cryoablation; IRE: Irreversible electroporation.

FOOTNOTES

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Postoperative adjuvant therapy for hepatocellular carcinoma with microvascular invasion

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Abstract

Hepatocellular carcinoma (HCC) is one of the most lethal tumors in the world. Liver resection (LR) and liver transplantation (LT) are widely considered as radical treatments for early HCC. However, the recurrence rates after curative treatment are still high and overall survival is unsatisfactory. Microvascular invasion (MVI) is considered to be one of the important prognostic factors affecting postoperative recurrence and long-term survival. Unfortunately, whether HCC patients with MVI should receive postoperative adjuvant therapy remains unknown. In this review, we summarize the therapeutic effects of transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy, tyrosine protein kinase inhibitor-based targeted therapy, and immune checkpoint inhibitors in patients with MVI after LR or LT, aiming to provide a reference for the best adjuvant treatment strategy for HCC patients with MVI after LT or LR.

Key Words: Microvascular invasion; Hepatocellular carcinoma; Liver resection; Liver transplantation; Postoperative; Adjuvant treatment

Core Tip: Microvascular invasion (MVI) is considered to be one of the important prognostic factors affecting postoperative recurrence and long-term survival. Unfortunately, whether hepatocellular carcinoma (HCC) patients with MVI should receive postoperative adjuvant therapy remains unknown. In this review, we summarize the therapeutic effects of transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy, tyrosine protein kinase inhibitor-based targeted therapy, and immune checkpoint inhibitors in patients with MVI after liver resection (LR) or liver transplantation (LT), aiming to provide a reference for the best adjuvant treatment strategy for HCC patients with MVI after LT or LR.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the second leading cause of cancer-related deaths in the world, with unsatisfactory long-term outcomes[1]. Nowadays, hepatectomy liver resection (LR) and liver transplantation (LT) are still the most efficient strategies for HCC with relatively preserved liver function[2]. Unfortunately, the surgical resection rate of HCC is still low in clinical practice due to untimely diagnosis and delayed treatment in most HCC patients. Even with radical surgery, the 5-year recurrence rate is still 70%-80%[3]. Accordingly, decreasing the recurrence rate after surgical resection is of utmost importance to improve the clinical outcomes for early-stage HCC patients.

Various risk factors are associated with the recurrence of HCC. Malignant biological characteristics of the tumor and the condition of the underlying liver disease, such as hepatitis and liver cirrhosis, were found to be more significant prognostic factors than tumor size and warrant closer attention in clinical practice[4]. Among malignant biological characteristics of HCC, microvascular invasion (MVI) is considered a risk factor for intrahepatic microscopic metastatic disease and one of the crucial factors for early HCC recurrence after LR or LT. As a consequence, In the 8th edition of the American Joint Committee on Cancer staging system, it was further included as an important prognostic factor, where it is considered an independent risk factor for poor clinical outcomes[5]. Currently, MVI is usually defined as tumor cells invading into the portal vein, hepatic vein, or a large capsular vessel of the surrounding tumor tissues, partially or totally lined by endothelial cells visible only by microscopical examination of specimens obtained from surgical excision, which is acknowledged as a histological feature[6]. MVI plays a crucial role in the selection of surgical modalities and also a vital indicator of early tumor recurrence in HCC patients[7]. Due to differences of MVI status, the surgical outcomes are likely inconsistent among different treatment groups. The presence of MVI in HCC is strongly correlated with the recurrence rates after surgical resection and should be classified as locally advanced-stage biological behavior[7,8]. Moreover, time to recurrence after curative surgical resection is a critical prognostic factor for clinical outcomes, as early tumor recurrence is associated with worse overall survival (OS). Therefore, postoperative adjuvant treatments may be partly beneficial to decrease the tumor recurrence rates in HCC patients with MVI. Unfortunately, there is still no consensus on the optimal adjuvant treatment after LR or LT for HCC with MVI.

Advances in systemic therapy for advanced HCC, as well as promising strategies for perioperative management of LR, have led to a substantial improvement of surgical outcomes in recent years. Transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), as well as targeted therapies based on tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors (ICIs), are the current state-of-the-art strategies, which have shown great promise in the treatment of advanced HCC[8-12]. However, whether TACE/HAIC, TKIs (such as sorafenib and lenvatinib), and ICIs [such as programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors] are beneficial for decreasing tumor recurrence rates in HCC patients with MVI remains controversial. In view of this, results derived from all the studies were analyzed, aiming to outline the optimal treatment strategy for HCC with MVI after LR. For patients with early-stage HCC, LR, LT, and local ablation (LA) are considered as first-line treatments. However, MVI cannot be precisely evaluated in HCC patients who underwent LA. Therefore, we mainly discuss the effect of postoperative treatments on the surgical outcomes after LT and LR. This review article aims to provide updated information on the recent developments in postoperative adjuvant therapy in HCC patients with MVI.

LR

MVI has been widely identified as a crucial risk factor for intrahepatic recurrence after R0 surgical resection, which was evidenced by increased local recurrence rates and reduced recurrence-free survival (RFS) after LR compared to HCC patients without MVI. Whether postoperative adjuvant therapy could improve the surgical outcomes for HCC with MVI remains unclear. There is an urgent need to discuss several postoperative adjuvant treatments such as TACE/HAIC and TKI and ICI therapy, aiming to shed a new light on ways to improve the prognosis for such HCC patients.

TACE

The main purpose of TACE after LR is to eliminate the tumor cells released due to compression during operation and destroy the existing microscopic foci in the remnant liver that cannot be found by preoperative imaging examination. It delivers specific drugs, along with iodized oil, mainly to suspected tumor areas, followed by embolization to cause tumor cell necrosis and prevent residual lesions from growing into clinically visible tumors. Some studies demonstrated a superior effect of postoperative TACE in terms of OS and RFS[13,14], while other studies reported comparable results with or without postoperative TACE[15,16]. The benefits of adjuvant TACE in HCC patients with MVI remain controversial. A meta-analysis indicted that adjuvant TACE plus LR may improve the surgical outcomes of HCC patients with MVI compared to LR alone and should be recommended for HCC patients with MVI[17]. Another meta-analysis showed that postoperative adjuvant HAIC could improve the long-term prognosis of HCC patients, especially those with microvascular or macrovascular invasion[18]. A retrospective study showed that postoperative HAIC offers better OS than simple surgical resection in patients with MVI[19]. The beneficial effect of postoperative adjuvant TACE may be related to a number of factors. First, the poor efficacy of surgical resection in patients with liver cancer complicated with MVI is due to the micrometastasis of residual cancer cells before or during LR [20,21]. Postoperative adjuvant TACE can kill or ablate these cells and improve the prognosis. Second, patients with MVI are prone to micrometastasis before surgery[22,23]. Therefore, TACE is a suitable and effective treatment 3-4 wk after LR, when the patients recover from surgery and the residual tumor is still small. Third, the majority of HCC blood supply comes from the hepatic artery, and recurrent tumors often occur near the edge of LR[24,25]. The use of postoperative adjuvant TACE increases the concentration of these marginal local anticancer drugs, which may improve the prognosis of such patients. However, there is no uniform standard for drug combination, dose, frequency of TACE, and time interval of each treatment. Nevertheless, other studies showed conflicting results. A meta-analysis of randomized clinical trials (RCTs) found that TACE did not improve RFS and OS after radical resection of HCC unless the tumor size was 5 cm[26]. A retrospective study showed that adjuvant HAIC using 5-fluorouracil and cisplatin did not improve disease-free survival (DFS) and OS after LR[27]. It remains unclear if HCC patients with MVI can benefit from adjuvant TACE treatment after surgery. The effectiveness of TACE may be due to the fact that chemotherapy drugs enter the blood vessels, and thereby come in contact with the migrating tumor cells to destroy them. However, due to the different tumor microenvironment and tumor heterogeneity in different populations, some patients still cannot benefit from this treatment. The tumor microenvironment may play a key role in the initiation and maintenance of drug resistance through various mechanisms such as pH changes, hypoxia, vascular system abnormalities, changes in immune populations, and extracellular matrix[28].

The pro-tumor environment that induces immunosuppression, such as myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages in the liver immune cell population, may play a major role in the limited effectiveness of chemotherapy drugs. Moreover, chemotherapy drugs themselves may change the composition of the inflammatory cell population[29]. In addition to the interaction of immune cells, hepatocirrhosis microenvironment composes a physical barrier that stimulates tumor growth by altering biomechanical properties, cytokine secretion, and activation of multiple signaling pathways, preventing drugs from reaching targets in the tumor parenchyma and thus reducing drug availability.

Moreover, high-dose TACE can damage liver cells, leading to the deterioration of liver function, reduced immunity against tumor cells, and increased risk of hepatitis B virus reactivation. In TACE, the combined use of multiple drugs may increase the burden on the liver leading to drug-induced liver injury, and ultimately adversely affect the therapeutic effect. Therefore, factors such as liver function and operation time should be considered in postoperative combined TACE treatment[19]. In addition, tumor load, tumor invasion, and postoperative recovery may be factors affecting the efficacy. The relevant studies on the postoperative application of TACE or HAIC as adjuvant therapy are listed in Table 1. However, these results need to be further verified by high-quality RCTs.

Target therapy-TKIs

Intrahepatic tumor recurrence after LR can be divided into early recurrence and late recurrence. Early recurrence is related to intrahepatic metastasis of primary tumors that cannot be detected clinically, which may be related to the spread and metastasis of tumor cells in portal vein circulation caused by the shedding of cancer cells before surgery or the pressure exerted on tumors during LR. As liver cancer

Table 1 Transcatheter arterial chemoembolization approved as an adjuvant therapy for hepatocellular carcinoma patients with microvascular invasion

Ref.	Study type	Adjuvant therapy	Number	2-yr DFS (%)	*P* value	2-yr OS (%)	*P* value	PMID
Li *et al*[17]	RCT	HAIC	63	58.7	0.023	97.7	0.037	32418078
		NAT	64	38.6		78.5		
Sun *et al*[72]	Retrospective	TACE	137	55.5	0.012	78.8	0.006	26714945
		NAT	185	36.2		62.2		
Wei *et al*[73]	RCT	TACE	125	44.7	0.02	64.3	0.029	30305149
		NAT	125	30.6		49.8		
Ye *et al*[13]	Retrospective	TACE	86	58.3	0.002	86.5	0.019	29151695
		NAT	174	41.1		65.7		
Liu *et al*[74]	Retrospective	TACE	24	26.9	0.03	NA	NA	27038790
		NAT	26	4.2		NA		
Wang *et al*[75]	Retrospective	TACE	57	66	0.008	94	0.04	30249510
		NAT	57	50		83		
Cai *et al*[76]	Retrospective	TACE	25	39.1	0.06	NA	NA	34926296
		TACE + T cell self	23	58.2		NA		
Kim *et al*[27]	RCT	HAIC	31	9.1	0.324	87.1	0.561	22067673
		NAT	62	4.2		78.3		
Nitta *et al*[77]	Retrospective	HAIC	38	33.1		56.2	0.318	23435678

DFS: Disease-free survival; OS: Overall survival; TACE: Transcatheter arterial chemoembolization; HAIC: Hepatic arterial infusion chemotherapy; NAT: No adjuvant therapy; NA: Not available; RCT: Randomized clinical trial.

cells gradually infiltrate the tumor capsule surrounding matrix, and vascular wall, they further invade blood vessels to form MVI. The multi-kinase inhibitors that target tumor cells and tumor blood vessels act on a variety of kinases and pro-angiogenic receptors, blocking downstream signaling pathways, inhibiting the proliferation and promoting apoptosis of tumor cells, as well as inhibiting tumor cell angiogenesis, and migration, with a wide range of anti-tumor effects that promote the prevention and treatment of tumor recurrence[30].

Sorafenib is a multi-kinase inhibitor that blocks multiple molecular pathways through its anti-angiogenic and anti-proliferative effects. A RCT revealed that sorafenib could effectively improve the survival time with advanced HCC patients[31]. In addition, sorafenib has been reported to inhibit postoperative intrahepatic recurrence and abdominal metastasis, thereby extending postoperative survival time[32,33].

Sorafenib can improve the prognosis of MVI in HCC patients after R0 LR. A meta-analysis investigated the preventive effect of sorafenib against tumor recurrence in HCC with MVI, and the results showed that LR plus sorafenib significantly improves the prognosis of HCC with MVI compared to LR alone. However, this meta-analysis has some shortcomings. First, it only included retrospective studies, which may cause selection bias. Second, the patients in these four studies were all Chinese, which also weakens the universality of the conclusion[34].

Recent studies have demonstrated the efficacy of sorafenib in preventing recurrence of HCC after LR [35]. Li *et al*[36] as well as Xia *et al*[37] found that the OS and DFS of Barcelona Clinic Liver Cancer stage C HCC patients treated with oral sorafenib after LR was significantly longer than those of patients only treated by LR. Wang *et al*[38] proved that sorafenib as an adjuvant therapy for HCC can prevent early recurrence after LR. Huang *et al*[39] evaluated the impact of sorafenib as an adjuvant therapy on the clinical outcomes in HCC with MVI. The results indicated that adjuvant sorafenib significantly prolonged both OS and RFS of patients with HCC after radical resection.

However, a RCT revealed that sorafenib treatment after LR did not improve the DFS of HCC patients, but increased the incidence of side effects, such as hand-foot skin reaction, diarrhea, and fatigue[40]. Similarly, it was found that postoperative sorafenib adjuvant therapy cannot improve RFS in HCC patients with MVI[41]. The relevant studies on postoperative application of TKIs as adjuvant therapy are listed in Table 2. There are differences in the results from different centers. In addition to the sample size and research methods that may affect the results, these differences may also be caused by different

Table 2 Tyrosine kinase inhibitor approved as an adjuvant therapy for hepatocellular carcinoma patients with microvascular invasion

NCT number	Title	Interventions	Characteristics	*n*	Date	Current status
NCT02678806	Radiotherapy in Hepatocellular Carcinomas After Hepatectomy With Narrow Margin (< 1 cm) and/or Microvascular Invasion (RHCC:BCLC-A)	Radiation: Postoperative radiotherapy. Drug: Postoperative TACE	Phase: Not applicable. Allocation: Randomized. Intervention model: Parallel. Outcome measures: Overall survival	620	November 1, 2017 to November 1, 2022	Recruiting
NCT04053972	The Impact on Recurrence Risk of Adjuvant Lenvatinib for Patients With Hepatocellular Carcinoma And Microvascular Invasion (MVI) After Hepatectomy: A Random, Controlled, Stage III Clinical Trial	Drug: Lenvatinib	Phase: 3. Allocation: Randomized. Intervention model: Parallel. Outcome measures: RFS and OS recurrence rate	377	January 31, 2018 to December 31, 2022	Recruiting
NCT02867280	Sorafenib Treatment in Patients With Hepatocellular Carcinoma With Microvascular Invasion After Radical Resection	Drug: Sorafenib	Phase: 3. Allocation: Non_x005f randomized. Outcome measures: Recurrence free survival; time to recurrence; recurrence rate; overall survival; incidence of treatment related; adverse events; incidence of dose modification of sorafenib due to adverse events	154	June 1, 2016 to January 31, 2020	Terminated
NCT03192618	The Impact on Recurrence Risk of Adjuvant Transarterial Chemoinfusion (TAI) for Patients With Hepatocellular Carcinoma And Microvascular Invasion (MVI) After Hepatectomy: A Random, Controlled, Stage III Clinical Trial	Procedure: Adjuvant transarterial chemoinfusion. Drug: mFOLFOX6 (oxaliplatin, calcium folinate, and 5-fluorouracil)	Phase: 3. Allocation: Randomized. Outcome measures: DFS; recurrence rate; OS	290	July 1, 2017 to December 31, 2024	Recruiting
NCT02436902	Adjuvant Therapies for Patients With HCC and MVI	Procedure: TACE. Drug: Sorafenib, TACE plus sorafenib and empty control	Phase: 3. Allocation: Non_x005f randomized. Outcome measures: Overall survivals; hospital mortality; recurrence rates	240	February 1, 2019 to August 30, 2022	Recruiting
NCT03732105	Radiotherapy/Apatinib for Adjuvant Treatment of HCC Patients receIved Curative resection With Microvascular Invasion	Radiotherapy. Drug: Apatinib and radiotherapy + apatinib	Phase: 2. Allocation: Randomized. Outcome measures: RFS; time to recurrence; overall survival; safety events; health related quality of life	160	November 1, 2018 to December 31, 2023	Not yet recruiting
NCT03575806	Combine TACE and Autologous Tcm Immunotherapy Versus TACE Alone for HCC With MVI After Radical Resection	Combination product: TACE plus autologous Tcm immunotherapy. Procedure: TACE	Phase: 2. Allocation: Non_x005f randomized. Outcome measures: RFS time; OS rate at 24 mo	52	January 9, 2017 to October 31, 2019	Completed
	Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy?	Drug: Sorafenib	Phase: Not applicable. Allocation: Retrospective study. Outcome measures: DFS; recurrence rate; OS	49	January, 2009 to December, 2016	Completed
	Microvascular Invasion as a Predictor of Response to Treatment with Sorafenib and Transarterial Chemoembolization for Recurrent Intermediate-Stage Hepatocellular Carcinoma	Procedure: TACE. Drug: Sorafenib, TACE plus sorafenib, and TACE	Phase: Not applicable. Allocation: Retrospective study. Outcome measures: DFS; recurrence rate; OS	127	January, 2010 to December, 2016	Completed
	Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis	Drug: Sorafenib	Phase: Not applicable. Allocation: Retrospective study. Outcome measures: DFS; recurrence rate; OS	728	January, 2009 to December, 2016	Completed
NCT00692770	Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial	Drug: Sorafenib	Phase: 3. Allocation: Randomized. Outcome measures: DFS; recurrence rate; OS	1114	August 15, 2008 to November 17, 2010	Completed

TACE: Transcatheter arterial chemoembolization; DFS: Disease-free survival; OS: Overall survival; RFS: Recurrence-free survival; HCC: Hepatocellular carcinoma; MVI: Microvascular invasion.

definitions and classifications of MVI. It may be necessary to conduct systematic research under uniform definitions and standards to make the results more comparable.

Although targeted drugs have greatly improved the prognosis of patients with advanced liver cancer, the efficacy of single drugs is still limited, and drug resistance may occur during treatment due to tumor heterogeneity and changes in the immune microenvironment. In addition, the side effects of drugs and the tolerance of patients also affect the therapeutic effect. In the future, it may be necessary to standardize the population suitable for targeted therapy, and consider combined therapy to improve the efficacy when single drugs are insufficient. In view of the above results, the role of targeted drugs as adjuvant therapy may still be controversial, and a large number of prospective RCTs are needed to further verify their efficacy in the future.

PD-1/PD-L1 treatment

ICIs are a new class of anti-tumor drugs that target regulatory signals between T cells, target cells, and other immune cells. T cells can recognize specific antigens presented on target cells by major histocompatibility complex proteins through their T cell receptors, and can induce apoptosis of target cells. T-cell activity is precisely regulated by co-stimulatory and co-inhibitory molecules to maintain an appropriate immune response without harmful overactivation. Therefore, adjuvant application of ICI after LR, may activate T cells to destroy circulating tumor cells and prevent recurrence.

At present, the main immune checkpoint molecules targeted by immunotherapy are PD-1, PD-L1, and cytotoxic T lymphocyte-associated protein 4. Cancer immunotherapy may have a significant impact in adjuvant settings, as it can immediately induce tumor cell killing and potentially produce durable immune responses that eliminate residual micrometastases that are thought to lead to early recurrence. Anti-PD-1/PD-L1 antibody, either alone or in combination, has shown successful induction of pathological reactions in a variety of tumor types, while also inducing tumor-specific T cell amplification, which may produce a vaccine effect capable of systemic monitoring[42,43]. The response rate to PD-1 blockade is about 20%, and the response to combined therapy may be higher[44,45].

At present, no large-scale clinical datasets have confirmed the role of ICIs in preventing postoperative recurrence and improving long-term survival in HCC. CheckMate-9DX is an ongoing trial investigating whether nivolumab can improve RFS compared with placebo in HCC patients who have a high risk of recurrence after LR or ablation, which includes patients with MVI.

Prevention of postoperative recurrence is an important part of the treatment of HCC, which is still an unsolved clinical problem. For early operable HCC with MVI, optimal liver function reserve, good physical condition, and increased tolerance to immune-related toxicity may improve the curative opportunity of the patients. However, the response of such patients to immunotherapy or drug resistance is still a challenge that cannot be ignored.

Considering the potential adverse reactions to combined administration, it is particularly important to select specific patients that most likely benefit from such therapies. Therefore, it is necessary to establish an effective predictive model, and a large number of prospective clinical studies are still needed to provide reliable guidance. In addition, there are studies on targeted drugs combined with immunotherapy for postoperative assistance, as shown in Table 3. We expect these effective research results to provide a reference for clinical decision-making. Since MVI is one of the critically important risk factors for relapse and metastasis, surgical resection alone may not completely eliminate the adverse effects of MVI and improve the prognosis of patients. Although there is no uniform standard for adjuvant therapy after LR, it may be one of the most promising strategies to improve the efficacy HCC therapy in patients with MVI.

LT

LT is suitable for patients with early HCC[46], but unfortunately, many patients are diagnosed at an advanced stage. Although many centers have expanded the indications beyond the Milan criteria and achieved promising results, there is still a high risk of relapse after transplantation, with HCC recurrence peaking about 2-3 years after LT[47-50].

Theoretically, LT completely eliminates tumors and potential lesions in the liver. However, MVI or undetected extrahepatic lesions can lead to HCC recurrence after transplantation. MVI was reported to be a major risk factor for HCC recurrence after LT[51]. Milan and other similar criteria are based on tumor size according to imaging, which does not provide sufficient information about pathological features and tumor biology, such as MVI and differentiation/grade. Therefore, these criteria cannot fully predict the recurrence of HCC after LT. MVI in the liver can predict tumor recurrence and indicate a poor prognosis. However, although MVI is an important predictor of tumor recurrence, without pathological examination, it is almost impossible to detect MVI before LT. Therefore, MVI largely determines the long-term prognosis of patients after resection and transplantation[52]. Theoretically, adjuvant therapy after LT may eradicate residual tumor cells in the blood. Therefore, it is very important to explore adjuvant therapy to improve the survival rate after transplantation.

At present, there is no systematic adjuvant therapy for HCC patients with MVI after transplantation, and most of the related studies focused on the treatment of recurrence after transplantation. Only some studies investigated adjuvant treatments for patients with a high risk of recurrence after transplantation

Table 3 Immune checkpoint inhibitors as an adjuvant therapy for hepatocellular carcinoma patients with microvascular invasion

NCT number	Title	Interventions	Characteristics	*n*	Date	Current status
NCT04682210	Sintilimab Plus Bevacizumab as Adjuvant Therapy in HCC Patients at High Risk of Recurrence After Curative Resection	Drug: Sintilimab. Drug: Bevacizumab	Phase: 3. Allocation: Randomized. Intervention model: Parallel	246	December, 2020 to December, 2024	Not yet recruiting
NCT04981665	A Study to Evaluate TACE Sequential Tislelizumab as Adjuvant Therapy in Participants With HCC at High Risk of Recurrence After Curative Resection	Drug: Tislelizumab. Drug: TACE	Phase: 2. Allocation: N/A. Intervention model: Single group assignment	50	November 8, 2021 to December, 2024	Recruiting
NCT05407519	A Study to Evaluate Tislelizumab Combined With Sitravatinib as Adjuvant Therapy in Participants With HCC at High Risk of Recurrence After Curative Resection	Drug: Tislelizumab. Drug: Sitravatinib	Phase: 2. Allocation: N/A. Intervention model: Single group assignment	52	July 25, 2022 to June 30, 2026	Recruiting
NCT04639180	A Study to Evaluate Camrelizumab Plus Rivoceranib (Apatinib) as Adjuvant Therapy in Patients With Hepatocellular Carcinoma (HCC) at High Risk of Recurrence After Curative Resection or Ablation	Drug: Camrelizumab.Drug: Rivoceranib (apatinib)	Phase: 3. Allocation: Randomized. Intervention model: Crossover assignment	674	April 1, 2021 to July 31, 2024	Recruiting
NCT03839550	Combine Apatinib Mesylate With PD-1 Antibody SHR-1210 for HCC With High Risk of Recurrence After Radical Resection	Drug: Apatinib Mesylate. Drug: SHR-1210	Phase: 2. Allocation: Randomized. Intervention model: Parallel	200	February 15, 2019 to February 28, 2023	Not yet recruiting
NCT03847428	Assess Efficacy and Safety of Durvalumab Alone or Combined With Bevacizumab in High Risk of Recurrence HCC Patients After Curative Treatment (EMERALD-2)	Drug: Durvalumab. Drug: Bevacizumab. Other: Placebo	Phase: 3. Allocation: Randomized. Intervention model: Parallel	908	April 29, 2019 to May 31, 2024	Not yet recruiting
NCT04102098	A Study of Atezolizumab Plus Bevacizumab Versus Active Surveillance as Adjuvant Therapy in Patients With Hepatocellular Carcinoma at High Risk of Recurrence After Surgical Resection or Ablation (IMbrave050)	Drug: Atezolizumab. Drug: Bevacizumab	Phase: 3. Allocation: Randomized. Intervention model: Parallel	668	December 31, 2019 to July 16, 2027	Not yet recruiting

TACE: Transcatheter arterial chemoembolization; HCC: Hepatocellular carcinoma.

beyond the Milan criteria. Nevertheless, patients with MVI were included in these studies, as summarized below and listed in Table 4.

There is a high burden of early immunosuppression, especially in the case of calcineurin inhibitors such as cyclosporine and tacrolimus, which are usually the basic drugs against organ rejection after transplantation and may also increase the risk of HCC recurrence[53-55]. By contrast, immunosuppressive regimens based on mammalian target of rapamycin inhibitors, such as sirolimus and everolimus, have antitumor properties *in vitro* and *in vivo* and may reduce the HCC recurrence rates. Unfortunately, a prospective phase III multicenter RCT showed no significant improvement of the recurrence rate in HCC transplant recipients treated with sirolimus[56].

Some small studies have shown that sorafenib can improve the survival rate of LT patients with a high risk of recurrence after transplantation[33], but there is also evidence against chemotherapy or sorafenib adjuvant therapy after LT[57]. Whether targeted drugs are suitable for LT patients with MVI therefore remains to be verified in the future. Overall, there is no evidence that systemic adjuvant chemotherapy after LT can prevent HCC recurrence[58].

Although ICIs have demonstrated a certain level of efficacy in advanced liver cancer, based on the characteristics of ICIs and the special physical condition of patients after LT, balancing graft-protective immunosuppression and anti-tumor immune enhancement is still an unresolved issue. The use of ICIs as adjuvant therapy in transplant recipients has been the subject of several case reports[58-62], but ICIs may promote allograft injury[63], leading to severe rejection and even death. When systematically evaluating the data of cancer transplant recipients receiving ICIs, 37.5% of the recipients experienced liver allograft rejection, resulting in a 75% incidence of end-stage organ failure[64]. PD-1 inhibitor therapy after LT was reported in eight cases, including two cases of graft rejection[58,60,65]. Even if the treatment strategy of combined ICIs has great prospects, clinicians should be extremely cautious in practical application.

Tumor cell invasion of microscopic blood vessels in the surrounding liver tissue adjacent to the tumor is a histological feature of HCC. In recent years, several studies have intended to classify MVI based on different features[66-68], indicating that MVI can be further classified as MI and microscopic portal vein invasion (MPVI)[69,70], where tumor cells may invade the microvessels at the initial stage of invasion, while the newly formed microvascular structure due to the interaction of liver tissue around the tumor

Table 4 Adjuvant therapy after liver transplantation

Ref.	Interventions	Characteristics	*n*	Result	PMID
Rodríguez-Perálvarez *et al* [53]	Drug: mTOR inhibitors	Multicenter retrospective study	219	Effective	23867318
Vivarelli *et al*[54]	Drug: Cyclosporine	Retrospective study	70	Effective	15838913
Vivarelli *et al*[55]	Drug: Tacrolimus	Retrospective study	139	Ineffective	18948815
Geissler *et al*[56]	Drug: Sirolimus	Phase: 3. Allocation: Randomized. Intervention model: Parallel	525	Ineffective	26555945
Friend *et al*[78]	Drug: Nivolumab	Retrospective study	2	Ineffective	28643391
Biondani *et al*[60]	Drug: Nivolumab	Case report	1	Ineffective	29293878
DeLeon *et al*[61]	Drug: PD-1/PD-L1 inhibitors	Retrospective study	7	Partly effective	30603124
Gassmann *et al*[63]	Drug: Nivolumab	Case report	1	Ineffective	30255136
Varkaris *et al*[65]	Drug: Pembrolizumab	Case report	1	Ineffective	29215617
Iavarone *et al*[79]	Drug: Sorafenib	Multicenter retrospective study	28	Ineffective	31365177

mTOR: Mammalian target of rapamycin; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1.

is defined as MI. Subsequently, as tumor invasion accelerates, tumor cells float and settle in the portal vein branches farther away from the original tumor, which is defined as MPVI. Unfortunately, MVI can only be definitively diagnosed by examining surgical specimens, limiting its role in guiding individualized treatment. The two types of MVI have different foundations and mechanisms. MPVI is a more advanced form of tumor invasion than MI. Patients with MPVI have more aggressive tumor characteristics, and the two different risk factors for recurrence suggest that the goals should be different when designing adjuvant therapy for each type. For MI, the main strategy should be targeted at disseminated tumor cells that spread from the primary tumor[7]. For MPVI, a potentially systemic treatment strategy is more appropriate. Our preliminary study indicated that postoperative adjuvant therapy could improve long-term outcomes after curative LR in HCC patients with MPVI, but the effect was weaker in MI. At the same time, our studies have shown that in MI, a wider surgical margin can eliminate peripheral intrahepatic micrometastasis, thereby preventing early tumor recurrence. By contrast, the surgical results of MPVI patients are similar regardless of the width of the surgical margin[71].

Therefore, it may not be wise to classify the two types of vascular invasion into one group for research and analysis, while more appropriate treatment strategies should be developed based on different biological and histological characteristics. Several limitations exist in this study. First, the prognosis of HCC is affected by a variety of factors including tumor markers, tumor size, tumor differentiation, and liver cancer staging, here, we only give a systematic review of the prognosis of patients with MVI, not considering other factors. Second, since adjuvant therapy after LT with MVI is relatively limited, the results obtained may not objectively reflect its efficacy. Third, we did not categorize all studies using meta-analysis, so there may still be valid treatment outcomes missed. Thus, more clinical studies may be needed to analyze the postoperative adjuvant therapy for such populations in order to obtain the best treatment strategy.

CONCLUSION

Adjuvant therapy for preventing tumor recurrence after radical resection in HCC patients with MVI is the key to improving the long-term survival rate. Although there is still controversy, after LR, TACE may be an effective choice to improve DFS and OS. As targeted therapy and immunotherapy have been effective in improving the prognosis of patients with advanced liver cancer in many retrospective studies, adjuvant therapy based on molecular targeted drugs needs further study. Many RCT studies evaluating adjuvant ICI after LR are ongoing, and their results may provide additional references for adjuvant therapy. In the future, prospective studies should be carried out to clarify the improvement of prognosis in the MVI subgroup by these two treatments. Moreover, in consideration of the actual drug efficacy, adverse reactions, and patient tolerance, the relationship between efficacy and safety should be balanced in clinical practice. It may be necessary to distinguish potential populations benefiting from each combination therapy, and to assess whether patients have the preconditions to receive effective combination therapy using novel biomarkers and biological characteristics.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic effect of excessive chemotherapy cycles for stage II and III gastric cancer patients after D2 + gastrectomy

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Abstract

BACKGROUND

According to relevant investigation and analysis, there are few research studies on the effect of excessive chemotherapy cycles after D2 gastrectomy on the survival of patients with gastric cancer.

AIM

To determine whether excessive chemotherapy cycles provide extra survival benefits, reduce recurrence rate, and improve survival rate in patients with stage II or III gastric cancer.

METHODS

We analyzed and summarized 412 patients with stage II gastric cancer and 902 patients with stage III gastric cancer who received D2 gastrectomy plus adjuvant chemotherapy or neoadjuvant chemotherapy. Analysis and comparison at a ratio of 1:1 is aimed at reducing realistic baseline differences (n = 97 in each group of stage II, n = 242 in each group of stage III). Progression-free survival, overall survival and recurrence were the main outcome indicators.

RESULTS

When the propensity score was matched, the baseline features of stage II and III gastric cancer patients were similar between the two groups. After a series of investigations, Kaplan-Meier found that the progression-free survival and overall survival of stage II and III gastric cancer patients were consistent between the two groups. The local metastasis rate (P = 0.002), total recurrence rate (P < 0.001) and

distant metastasis rate (P = 0.001) in the ≥ 9 cycle group of stage III gastric cancer were statistically lower than those in the < 9 cycle group. The interaction analysis by Cox proportional hazard regression model showed that intestinal type, proximal gastrectomy, and ≥ 6 cm maximum diameter of tumor had a higher risk of total mortality in the < 9 cycles group.

CONCLUSION
Overall, ≥ 9 chemotherapy cycles is not recommended for patients with stage II and stage III gastric cancer because it has an insignificant role in the prognosis of gastric cancer. However, for patients with stage III gastric cancer, ≥ 9 cycles of chemotherapy was shown to significantly decrease recurrence.

Key Words: Gastric cancer; Propensity score matching; Chemotherapy cycles; Overall survival; Progression-free survival; Recurrence

Core Tip: This retrospective study determined the survival benefit of excess chemotherapy cycles for gastric cancer after D2 gastrectomy. No difference in progression-free survival and overall survival was observed between patients receiving ≥ 9 or < 9 cycles of chemotherapy. Stage III gastric cancer patients receiving ≥ 9 cycles of chemotherapy had significantly lower overall recurrence, local-regional metastasis, and distant metastasis. The Cox proportional risk regression model was used in the exploration and analysis that intestinal type, proximal gastrectomy, and ≥ 6 cm maximum tumor diameter had a higher risk of total mortality in the < 9 cycles of chemotherapy group.

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INTRODUCTION

Common cancer cases in the world include gastric cancer which is also the main cause of human cancer death[1]. Specifically, gastric cancer, one of the most common cancers in the world, has a survival rate of only 20%. Stomach cancer is a malignant tumor in which cancer cells attach to the gastric mucosa and gradually spread throughout the body. At the beginning, there are no special symptoms of gastric cancer and the patient is unaware of the problem. However, with the extension of time and the deterioration of the disease, patient's stomachs are gradually unable to digest, causing discomfort. In the final stages, gastric cancer patients will vomit, experience pain, and in severe cases will cough up blood. They present with abdominal swelling, lymph node metastasis and so on. According to the relevant data, the production of gastric cancer is affected by different factors. The initial symptom may be chronic gastritis or bacterial infection, or the gastrointestinal discomfort caused by genes and adverse environment, which may turn into gastric cancer. Among them, the most important factor affecting the occurrence of gastric cancer is the bad environment. If the soil or water contains excessive nitrate and other chemical elements, it is very likely to lead to the occurrence of gastric cancer, and people will inevitably ingest these elements during the diet. In daily life, salty food can also lead to stomach cancer. Moldy food can also cause stomach cancer if consumed for a long time. Generally speaking, the incidence of gastric cancer in women is much lower than that in men, and the most important type of gastric cancer is adenocarcinoma, including diffuse gastric cancer and intestinal gastric cancer. The older people are, the more likely they are to develop stomach cancer, ranging in age from 50 to 80. The incidence of stomach cancer of our people is not low in the global scope, and is far higher than the world average level. Stomach cancer accounts for nearly a quarter of cancer deaths. In the early stages of gastric cancer, when there is no lymphatic metastasis, endoscopic treatment is recommended. In the middle stage of gastric cancer, when the cancer cells are not yet spreading throughout the body, it can be treated by D2 gastrectomy. After the tumor is removed, adjuvant therapy is given postoperatively to reduce the likelihood of bacterial infection and avoid the risk of death.

Although D2 gastrectomy and postoperative adjuvant therapy are the only radical methods for the treatment of gastric cancer at this stage, patients with stage II and III gastric cancer have a higher recurrence rate after surgery and do not have a higher long-term survival rate. In academia, experts and scholars have discussed the value and effect of postoperative adjuvant chemotherapy for gastric cancer. With the development of the times and the progress of society, more and more people analyze the

influence of postoperative adjuvant therapy on gastric cancer patients through experiments and research contents. In this context, people increasingly affirm the value of postoperative adjuvant chemotherapy for gastric cancer. According to relevant data, postoperative adjuvant chemotherapy reduced the mortality rate by more than 20% compared with surgery alone. Therefore, the comprehensive treatment mode of surgery combined with adjuvant chemotherapy has been used more frequently in the treatment of gastric cancer. However, at present, the duration of adjuvant therapy after radical gastrectomy has not been determined, and the correlation between the length of chemotherapy cycles and the effect of chemotherapy is not clear. In other words, with the development of the times, D2 gastrectomy[2] and subsequent adjuvant chemotherapy are constantly improved, and the overall survival period (OS) of gastric cancer patients has been well transformed, but from the perspective of long-term survival, there are still limitations[3,4].

Excessive chemotherapy cycles to treat gastric cancer has been proposed, but the survival benefit has not been determined. According to the Chinese Society of Clinical Oncology clinical guidelines[5] for the diagnosis and treatment of gastric cancer, preoperative neoadjuvant chemotherapy is recommended for 2-4 cycles, and perioperative neoadjuvant chemotherapy is recommended for 2-4 cycles before surgery and 6-8 cycles after surgery. Therefore, ≥ 9 cycles of chemotherapy would be considered as excessive chemotherapy cycles.

In our previous study[6] of patients with stage II and stage III gastric cancer, the mean of chemotherapy cycles was 9.65 ± 3.86 and 9.87 ± 3.84, respectively. In addition, we analyzed 1-, 3- and 5-year survival rates for patients receiving < 9 cycles of chemotherapy, and found them to be 92.4% (257/278), 66.9% (186/278), and 46.4% (129/278), respectively. The 1-, 3-, and 5-year survival rates for patients receiving ≥ 9 cycles of chemotherapy were found to be 92.5% (577/624), 62.9% (393/624), and 46.3% (289/624), respectively.

In essence, chemotherapy can be both good and bad for patients. Excessive chemotherapy cycles (≥ 9) give rise to unpleasant side effects and harmful effects on physical function. However, the appropriate number of chemotherapy cycles may eliminate any residual cancer cells. The ultimate aim of our research was to determine whether excessive chemotherapy cycles (≥ 9) increase survival and decrease recurrence in patients with stage II and III gastric cancer.

MATERIALS AND METHODS

Data collection

We summarized the relevant data from 2002 to 2020 of more than 400 patients with stage II gastric cancer and 900 patients with stage III gastric cancer who underwent gastrectomy for the treatment of gastric cancer. According to the data, lymph node dissection was higher than D2 (complete removal of group 1 and group 2 Lymph nodes). The clinicopathological characteristics included age at surgery, sex, nerve invasion, vascular invasion, number of positive lymph nodes, depth of tumor invasion, number of chemotherapy cycles, TNM stage (according to the 8th edition of the American Joint Board on Cancer), maximum tumor diameter, Lauren classification, retinal metastasis, type of gastrectomy, chemotherapy administration, surgical margin, multi-organ resection, chemotherapy protocol, and group Clavien-Dindo grading of texture, multiple metastases, OS, complications, and progression-free survival (PFS). The number of postoperative chemotherapy cycles, the number of neoadjuvant chemotherapy cycles, medical records, surgical records and follow-up data were analyzed retrospectively.

The inclusion criteria consisted of: (1) Neoadjuvant chemotherapy or adjuvant chemotherapy before radical gastrectomy; (2) Histologically proven gastric cancer; (3) There was no serious damage to the organs after the operation; (4) Complete clinicopathological and follow-up data; and (5) Except for gastric cancer, there were no other malignancies or causes of death. Exclusion criteria are classified as follows: (1) There is no complete clinical data; (2) Other systemic tumors; (3) Non gastric cancer was confirmed by pathological classification; and (4) Bypass surgery and palliative surgery.

The American Joint Board on Cancer's 8 TNM grade reclassified tumor stages. Because this study is retrospective, consent is not required. After a series of reviews, the Ethics Committee of Shanxi Cancer Hospital finally approved the study. This study was consistent with the standards of the Declaration of Helsinki, so patient anonymity was adopted and patient data and information were not disclosed to the public. The specific research content and process are shown in Figure 1.

Patients received individualized chemotherapy regimens. This paper summarized the dose ranges and other details of several common regimens: (1) Oxaliplatin (130 mg/m^2), S-1 and oxaliplatin (SOX), S-1 (40-60 mg), the above-mentioned drugs twice a day, the 1st to 14th d, rest for 7 d; (2) S-1, the aforementioned drug twice daily, with the specific dose schedule determined by the patient's area. From day 1 to day 14, 40-60 mg, then rest for 7 d; (3) S-1 + apatinib, apatinib (500 mg) administered once daily continuously and S-1 (40-60 mg) administered twice daily on day 1 to day 14, then rest for 7 d; (4) Folinic acid, fluorouracil, and oxaliplatin (FOLFOX), folinic acid (200 mg/m^2), fluorouracil (2800 mg/m^2), and oxaliplatin (85 mg/m^2) administered every 3 wk; (5) Oxaliplatin and capecitabine (also known as XELOX) were given intravenous oxaliplatin (150 mg/m^2) on the 1st day of every three cycles and orally capecitabine (1000 mg/m^2) twice a day from day 1 to day 14, followed by a rest for 7 d; (6)

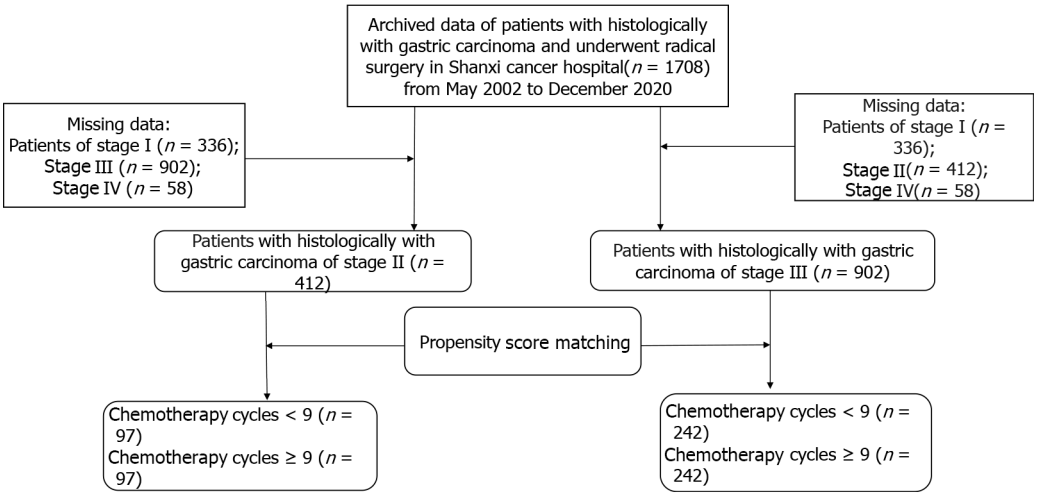

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Figure 1 Flowchart of study population enrollment.

Capecitabine was taken orally twice a day (1000 mg/m^2), with a rest of 7 days from day 1 to day 14; (7) Cisplatin and fluorouracil (also known as DCF), S-1 + docetaxel, cisplatin (75 mg/m^2), docetaxel (75 mg/m^2) on day 1 to day 5, fluorouracil (750 mg/m^2) on day 1 to day 5, S-1 (40-60 mg) on day 1 to day 14, orally twice a day, then rest for 7 d; and (8) Oral administration of defluoruridine (1000 mg/m^2) twice a day from day 1 to day 28, followed by rest for 14 d.

All excised specimens were examined to determine the histological response to neoadjuvant chemotherapy and pathological staging. The number of surviving tumor cells in the tumor determines the grade of tumor regression. According to Ryan criteria[6]: Grade 0 (complete response), no residual tumor cells. Grade 1 (primary remission), with scattered tumor cells; Grade 2 (moderate remission), tumor cell aggregation with fibrosis; Grade 3 (mild remission), with substantial tumor cell retention. The toxicity associated with neoadjuvant chemotherapy was evaluated according to Standard 5.0, a common term for adverse events[7].

Follow-up

Patients were followed up until December 2020. The second-stage follow-up was 41.51 ± 21.18 mo, and the third-stage follow-up was 43.56 ± 24.45 mo. Follow-up was conducted every 3 mo for 1 year after surgery, every 6 mo for 2 years to 5 years, and annually thereafter. Routine follow-up included laboratory tests, physical examinations, pelvic ultrasound, chest radiographs, magnetic resonance imaging, and computed tomography.

Statistical analyses

Sex, age at surgery, vascular invasion, nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, type of gastrectomy, and human epidermal growth factor receptor-2 (HER2) status were used for propensity score matching (PSM) using 1:1 nearest neighborhood with no replacement and calipers adjusted for sample size and matching success. If a patient is a match, a correlation analysis of primary and secondary endpoints will be performed. The main contents are PFS and OS. The secondary endpoints were tumor recurrence and metastasis, multiple metastases, and recurrence patterns.

Each group generated a Kaplan-Meier survival curve using a log-rank comparison. The category variable analysis was tested using appropriate tests. The *P* values on both sides were 0.05, which had statistical value. The date of return visit is calculated from the date of surgery to the time of last contact. OS is the time between surgery and death or the last follow-up. PFS refers to the time between surgery and the first recorded death or recurrence.

All data were analyzed and explored using SPSS v25.0 software (IBM Corp., Armonk, NY, United States). The classification variable was expressed as percentage, and the test methods used in the analysis were Fisher's exact test and chi-square test. Continuous data were expressed as mean ± standard deviation, and *t*-test was used for analysis. Survival analysis of PFS and OS was performed using Kaplan-Meier method, which was compared with the log-rank test method. Median was used for the non-normal distribution parameters, and the analysis method was Mann-Whitney test. Subgroup analyses were performed by the Cox hazard regression model. $P < 0.05$ was considered statistically significant. PSM was performed with the Hansen and Bowers overall balance test. Relative multivariate imbalance L1 test was used to determine standardized mean difference < 0.25. The χ^2 test was used to compare the differences in recurrence, local-regional recurrence, peritoneal metastasis, and distant

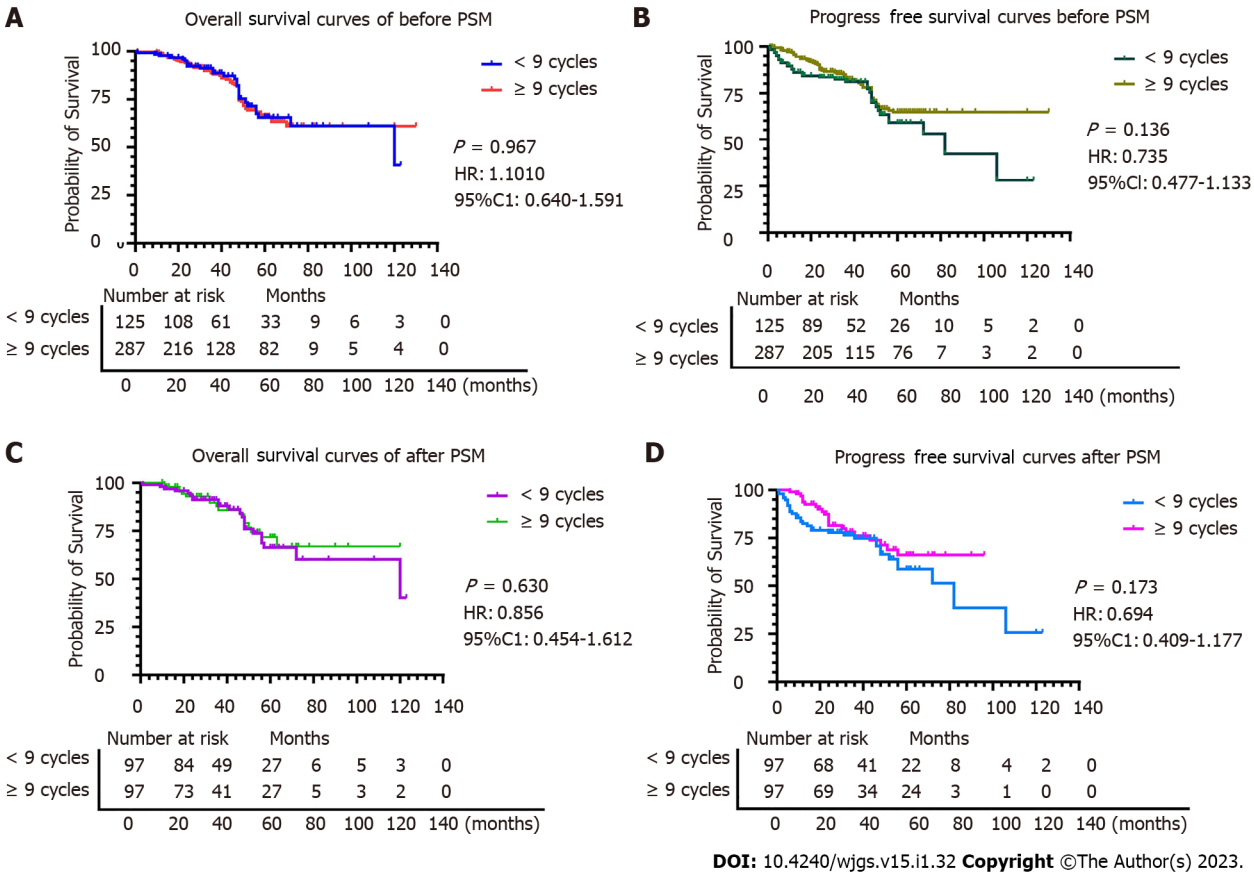

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Figure 2 Comparison of overall survival and progression-free survival before and after propensity score matching in stage II gastric cancer patients. A: Comparison of overall survival between the two groups based on chemotherapy cycles before propensity score matching (PSM); B: Comparison of progression-free survival between the two groups based on chemotherapy cycles before PSM; C and D: Comparison of overall survival (C) and progression-free survival (D) between the two groups based on chemotherapy cycles after PSM.

metastasis between the two groups.

Nonetheless, the interaction effect between chemotherapy cycles and Lauren classification, types of gastrectomy, and maximum diameter of the tumor on OS were determined for the first time.

RESULTS

PSM and subgroup analysis of TNM stage II gastric cancer patients

Patients in the < 9 cycles group received the following chemotherapy regimens: (1) 1 patient received S-1; (2) 28 patients received SOX; (3) 4 patients received S-1 + docetaxel; (4) 10 patients received deofuridine; (5) 3 patients received XELOX; (6) 32 patients received FOLFOX; and (7) 18 patients received multiple regimen combinations. Patients in the ≥ 9 cycles group received the following chemotherapy regimens: (1) 61 patients received S-1; (2) 6 patients received SOX; (3) 9 patients received S-1 + apatinib; (4) 15 patients received capecitabine; (5) 2 patients received FOLFOX; and (6) 5 patients received multiple regimen combinations. Three patients in the < 9 cycles group and 21 patients in the ≥ 9 cycles group received neoadjuvant chemotherapy plus adjuvant chemotherapy. Ninety-four patients in the < 9 cycles group and 76 patients in the ≥ 9 cycles group received only postoperative adjuvant chemotherapy.

All patients with TNM stage II (n = 412) were grouped based on nine variables (sex, vascular invasion, nerve invasion, number of positive lymph nodes, depth of tumor invasion, maximum tumor diameter, Lauren classification, type of gastrectomy, and HER2 status) according to the cycles of chemotherapy received (< 9 cycles *vs* ≥ 9 cycles) (Table 1). Significant differences in sex (P = 0.022) and age (P < 0.001) were observed between the < 9 cycles group *vs* the ≥ 9 cycles group before PSM. However, after PSM, in which 194 patients were included (97 patients in the <9 cycles group and 97 patients in ≥ 9 cycles group), no significant differences were observed between the two groups (P > 0.05). The Hansen and Bowers overall balance test indicated that the distribution between the two groups was well balanced after PSM (Figures 2 and 3).

Table 1 Patient characteristics before and after propensity score matching based on the number of chemotherapy cycles for stage II gastric cancer

Variables	Before PSM		*P* value	After PSM		*P* value
	< 9 cycles, *n* = 125	≥ 9 cycles, *n* = 287		< 9 cycles, *n* = 97	≥ 9 cycles, *n* = 97	
Sex			0.022			0.718
Male	95	245		77	79	
Female	30	42		20	18	
Age in yr	55.38 ± 10.91	60.44 ± 9.85	< 0.001	56.46 ± 10.10	56.46 ± 10.10	0.215
Depth of tumor invasion			0.248			0.998
T1	7	6		5	4	
T2	11	18		10	10	
T3	79	195		60	62	
T4	28	68		22	21	
Number of positive lymph nodes			0.064			0.740
0	64	172		52	49	
1-2	53	107		39	43	
3-6	4	5		4	3	
≥ 7	4	3		2	2	
Type of gastrectomy			0.448			0.249
Proximal	14	24		10	8	
Distal	41	93		32	26	
Total	0	170		55	63	
Vascular invasion			0.561			0.468
Negative	77	168		54	59	
Positive	48	119		42	38	
Neural invasion			0.719			1.000
Negative	79	176		64	64	
Positive	46	111		33	33	
Lauren classification			0.793			0.493
Intestinal	60	143		47	52	
Diffuse	27	58		21	19	
Mixed	38	86		29	26	
Maximum diameter of tumor in cm			0.603			0.410
< 6	87	207		70	75	
≥ 6	38	80		27	22	
Surgical margin			0.740			0.562
Negative	123	281		95	96	
Positive	2	6		2	2	
HER2			0.337			0.911
Negative	70	171		55	54	
Positive	55	116		42	43	

PSM: Propensity score matching.

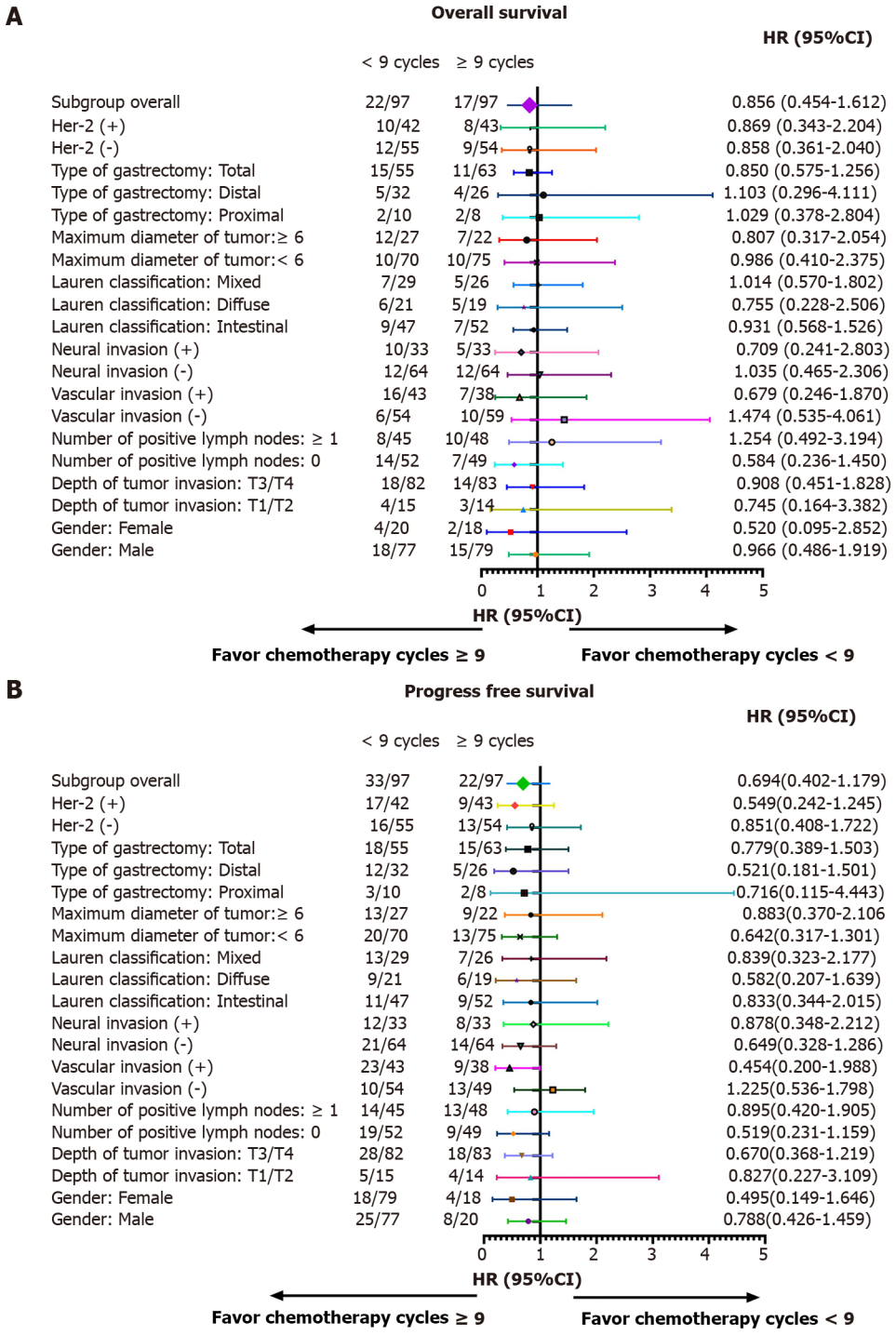

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Figure 3 Subgroup analysis of overall survival and progression-free survival based on chemotherapy cycles in stage II gastric cancer patients. A: Overall survival; B: Progression-free survival.

OS and PFS were similar in both groups before and after PSM ($P > 0.05$), indicating that in patients with stage II gastric cancer ≥ 9 chemotherapy cycles does not impart a survival benefit (Figures 2 and 3). In detail, the 1-year OS rate (96.9% *vs* 97.9%, log-rank $P = 0.650$), 3-year OS rate (89.7% *vs* 89.7%, log-rank $P = 1.000$), and 5-year OS rate (79.4% *vs* 83.5%, log-rank $P = 0.460$) were not statistically different. The 1-year PFS rate was statistically different between the ≥ 9 cycles group and the < 9 cycles group (93.8% *vs* 82.4%, log-rank $P = 0.015$, respectively). However, that benefit was not observed in the 3-year PFS rate (76.3% *vs* 81.4%, log-rank $P = 0.379$) and in the 5-year PFS rate (69.1% *vs* 77.3%, log-rank $P = 0.195$). No differences were observed between the < 9 cycles group and the ≥ 9 cycles group for recurrence (22.7% *vs* 12.4%, respectively, $P = 0.059$), local-regional metastasis (11.3% *vs* 11.3%, respectively, $P = 0.117$), and distant metastasis (5.2% *vs* 6.2%, respectively, $P = 0.204$).

Table 2 Subgroup analysis of overall survival by Cox regression analysis of stage II gastric cancer patients

Variables	Death	Total	HR	95%CI	*P* value	*P* for interaction
Sex						0.219
Male	33	156	0.966	0.486-1.919	0.922	
Female	6	38	0.520	0.095-2.852	0.452	
Depth of tumor invasion						0.749
T1/T2	7	29	0.745	0.164-3.382	0.702	
T3/T4	32	165	0.908	0.451-1.828	0.786	
Number of positive lymph nodes						0.458
0	21	101	0.584	0.236-1.450	0.247	
≥ 1	18	93	1.254	0.492-3.194	0.635	
Vascular invasion						0.729
Negative	24	128	1.474	0.535-4.061	0.431	
Positive	15	66	0.679	0.246-1.870	0.453	
Neural invasion						0.937
Negative	36	163	1.035	0.465-2.306	0.932	
Positive	22	93	0.709	0.241-2.083	0.531	
Lauren classification						0.553
Intestinal	16	99	0.931	0.568-1.526	0.766	
Diffuse	11	40	0.755	0.228-2.506	0.647	
Mixed	12	55	1.014	0.570-1.802	0.963	
Maximum diameter of tumor in cm						0.167
< 6	20	145	0.986	0.410-2.375	0.976	
≥ 6	19	49	0.807	0.317-2.054	0.653	
Type of gastrectomy						0.664
Proximal	4	18	1.029	0.378-2.804		
Distal	9	58	1.103	0.296-4.111		
Total	26	118	0.850	0.575-1.256		
HER2						0.656
Negative	21	109	0.858	0.361-2.040		
Positive	18	85	0.869	0.343-2.204		

CI: Confidence interval; HR: Hazard ratio.

We performed subgroup analyses according to depth of tumor invasion, sex, vascular invasion, number of positive lymph nodes, Lauren classification, neural invasion, types of gastrectomy, maximum diameter of tumor, and HER2 in order to determine if a survival benefit of ≥ 9 cycles was evident in specific patient populations. After subgroup analysis, the differences in OS and PFS between the two groups were not statistically significant (Tables 2 and 3, and Figure 3).

PSM and subgroup analysis of TNM stage III gastric cancer patients

Patients in the < 9 cycles group received the following chemotherapy regimens: (1) 5 patients received S-1 + apatinib; (2) 4 patients received S-1 + DCF; (3) 10 patients received SOX + FOLFOX; (4) 4 patients received S-1 + FOLFOX; (5) 8 patients received XELOX; (6) 98 patients received FOLFOX; and (7) 18 patients received multiple regimen combinations. Patients in the ≥ 9 cycles group received the following chemotherapy regimens: (1) 142 patients received S-1; (2) 2 patients received SOX; (3) 2 patients received S-1 + DCF; (4) 29 patients received capecitabine; (5) 9 patients received doxifluridine; (6) 6 patients received SOX + FOLFOX; (7) 2 patients received FOLFOX; and (8) 50 patients received multiple regimen combinations. Twenty-four patients in the < 9 cycles group and forty-one patients in the ≥ 9 cycles

Table 3 Subgroup analysis of progression-free survival by Cox regression analysis of chemotherapy cycles of stage II gastric cancer

Variables	Death or recurrence	Total	HR	95%CI	*P* value	*P* for interaction
Sex						0.385
Male	33	156	0.788	0.426-1.459	0.449	
Female	22	38	0.495	0.149-1.646	0.252	
Depth of tumor invasion						0.226
T1/T2	9	29	0.827	0.227-3.109	0.779	
T3/T4	46	165	0.670	0.368-1.219	0.190	
Number of positive lymph nodes						0.842
0	28	101	0.519	0.232-1.159	0.110	
≥ 1	27	93	0.895	0.420-1.905	0.773	
Vascular invasion						0.743
Negative	23	128	1.225	0.536-1.798	0.630	
Positive	32	66	0.454	0.200-0.988	0.047	
Neural invasion						0.732
Negative	35	163	0.649	0.328-1.286	0.216	
Positive	20	93	0.878	0.348-2.212	0.782	
Lauren classification						0.622
Intestinal	20	99	0.833	0.344-2.015	0.685	
Diffuse	15	40	0.582	0.207-1.639	0.306	
Mixed	20	55	0.839	0.323-2.177	0.718	
Maximum diameter of tumor in (cm)						0.128
< 6	33	145	0.642	0.317-1.301	0.219	
≥ 6	22	49	0.883	0.370-2.106	0.779	
Type of gastrectomy						0.356
Proximal	5	18	0.716	0.115-4.443	0.720	
Distal	17	58	0.521	0.181-1.501	0.227	
Total	35	118	0.779	0.389-1.503	0.483	
HER2						0.200
Negative	29	109	0.851	0.408-1.772	0.665	
Positive	26	85	0.549	0.242-1.245	0.151	

CI: Confidence interval; HR: Hazard ratio.

group received neoadjuvant chemotherapy plus adjuvant chemotherapy. Two hundred eighteen patients in the < 9 cycles group and two hundred and one patients in the ≥ 9 cycles group received only postoperative adjuvant chemotherapy.

All patients with TNM stage III (n = 902) were grouped based on nine variables (sex, vascular invasion, nerve invasion, number of positive lymph nodes, depth of tumor invasion, maximum tumor diameter, Lauren classification, type of gastrectomy, and HER2 status) according to the cycles of chemotherapy received (< 9 cycles *vs* ≥ 9 cycles). Significant differences in age (P < 0.001) and type of gastrectomy (P = 0.044) were observed between the < 9 cycles group and the ≥ 9 cycles group before PSM. After PSM, in which 484 patients were included (there were 242 patients in the ≥ 9 cycle group and 242 patients in the < 9 cycle group), differences were observed between variables in the two groups (P > 0.05). The Hansen and Bowers overall balance test indicated that the distribution between the two groups was well balanced after PSM (Table 4, Figures 4 and 5).

OS and PFS were similar in both groups before and after PSM (P > 0.05), indicating that in patients with stage III gastric cancer ≥ 9 chemotherapy cycles does not impart a survival benefit (Figures 4 and 5). In detail, the 1-year OS rate (91.7% *vs* 92.5%, log-rank P = 0.735), 3-year OS rate (67.4% *vs* 63.6%, log-

Table 4 Patient characteristics before and after propensity score matching based on the number of chemotherapy cycles for stage III gastric cancer

Variables	Before PSM		*P* value	After PSM		*P* value
	< 9 cycles, *n* = 278	≥ 9 cycles, *n* = 624		< 9 cycles, *n* = 242	≥ 9 cycles, *n* = 242	
Sex			0.082			0.298
Male	207	497		185	175	
Female	71	127		57	67	
Age in yr	56.97 ± 9.85	59.91 ± 10.03	< 0.001	57.35 ± 9.31	58.01 ± 9.17	0.418
Depth of tumor invasion			0.568			0.754
T2	1	1		0	0	
T3	72	152		60	63	
T4	205	471		182	179	
Number of positive lymph nodes			0.110			0.756
0	0	4		0	0	
1-2	39	111		36	34	
3-6	68	155		60	67	
≥ 7	171	354		146	141	
Type of gastrectomy			0.044			0.903
Proximal	16	36		13	12	
Distal	89	154		71	71	
Total	173	454		158	159	
Vascular invasion			0.852			0.916
Negative	67	154		59	60	
Positive	211	470		183	182	
Neural invasion			0.156			0.288
Negative	85	211		74	85	
Positive	193	403		168	157	
Lauren classification			0.664			0.597
Intestinal	52	125		46	42	
Diffuse	153	315		127	127	
Mixed	73	184		69	73	
Maximum diameter of tumor in cm			0.346			0.467
< 6	134	322		119	111	
≥ 6	144	302		123	131	
Surgical margin			0.571			0.254
Negative	260	577		225	218	
Positive	18	47		17	24	

PSM: Propensity score matching.

rank P = 0.389), and 5-year OS rate (47.1% *vs* 42.5%, log-rank P = 0.315) were not statistically different. The 1-year and 3-year PFS rates in the ≥ 9 period group and the <9 period group were statistically significant (80.1% *vs* 62.0%, log-rank P < 0.001, respectively, and 44.2% *vs* 54.5%, log-rank P = 0.023, respectively). However, that benefit was not observed in the 5-year PFS rate (38.4% *vs* 33.9%, log-rank P = 0.298). We observed that ≥ 9 chemotherapy cycles can significantly reduce the probability of recurrence compared to < 9 chemotherapy cycles (24.4% *vs* 48.8%, respectively, P < 0.001), local-regional

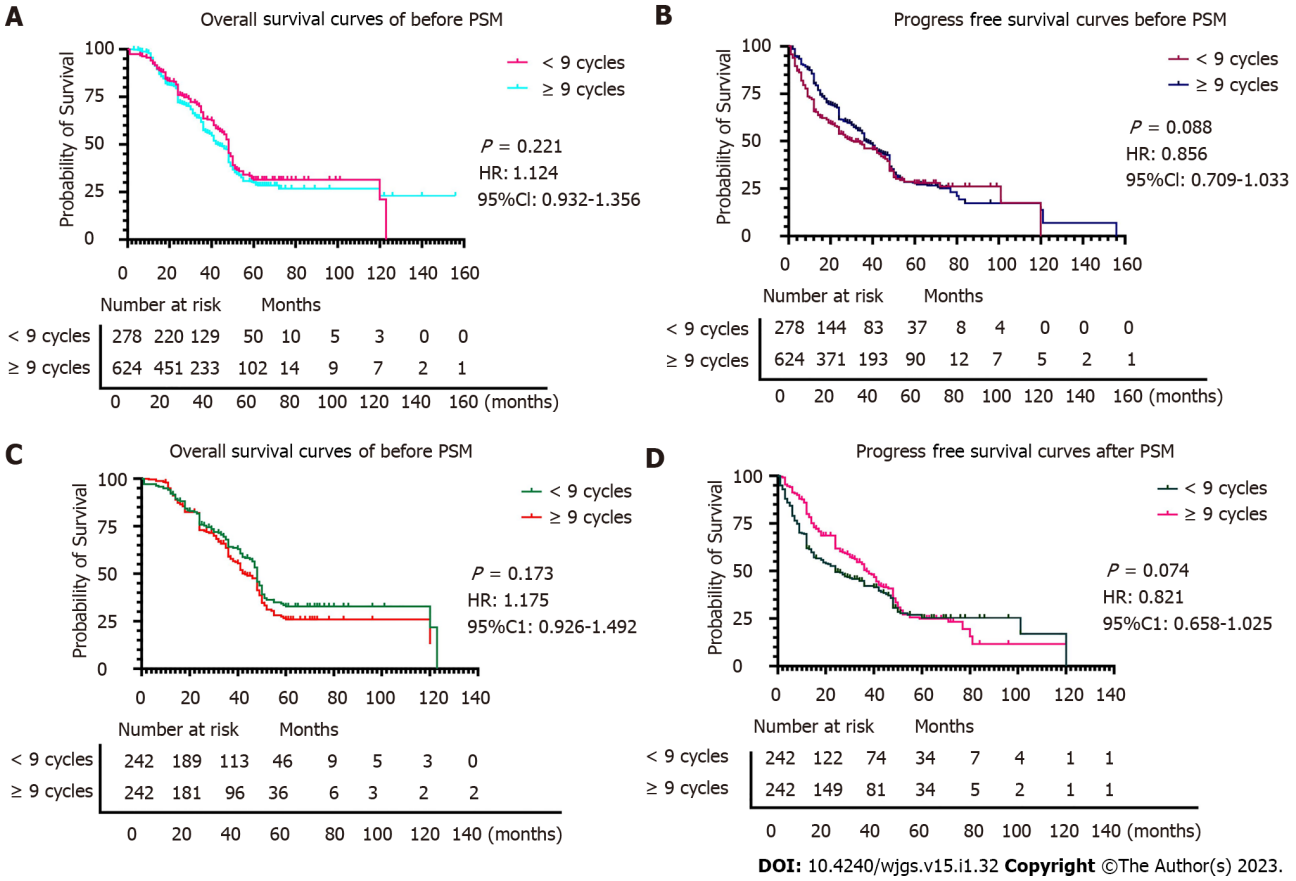

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Figure 4 Comparison of overall survival and progression-free survival before and after propensity score matching in stage III gastric cancer patients. A: Comparison of overall survival between the two groups based on chemotherapy cycles before propensity score matching (PSM); B: Comparison of progression-free survival between the two groups based on chemotherapy cycles before PSM; C and D: Comparison of overall survival (C) and progression-free survival (D) between the two groups based on chemotherapy cycles after PSM.

metastasis (10.7% *vs* 21.1%, respectively, $P = 0.002$), and distant metastasis (12.4% *vs* 24.0%, respectively, $P = 0.001$) but not peritoneal metastasis (1.2% *vs* 3.7%, respectively, $P = 0.090$).

We performed subgroup analyses according to depth of tumor invasion, sex, vascular invasion, neural invasion, number of positive lymph nodes, maximum diameter of tumor, Lauren classification, types of gastrectomy, and HER2 in order to determine if a survival benefit of ≥ 9 cycles was evident in specific patient populations. The analyses demonstrated that the ≥ 9 chemotherapy cycles group had increased OS compared to the < 9 chemotherapy cycles for most subgroups (Table 5). Significant interactions were observed between chemotherapy cycles and the number of positive lymph nodes (P for interaction = 0.007), Lauren classification (P for interaction = 0.002), type of gastrectomy (P for interaction = 0.004), and maximum tumor diameter (P for interaction < 0.001).

After further interaction subgroup analyses, patients with ≤ 6 positive lymph nodes [hazard ratio (HR): 1.312, 95% confidence interval (CI): 0.867-1.988], with intestinal type (HR: 1.196, 95%CI: 0.873-1.640), receiving proximal gastrectomy (HR: 1.175, 95%CI: 0.680-2.032), with ≥ 6 cm maximum diameter of tumor (HR: 1.240, 95%CI: 0.909-1.692) showing a higher risk of total mortality in the < 9 cycles group compared with the ≥ 9 cycles group (Table 6).

DISCUSSION

According to relevant data, the literature shows that the number of chemotherapy cycles received by patients is associated with the prognosis. A study conducted in China showed that patients with triple-negative breast cancer who received at least four chemotherapy cycles had a significantly better survival rate[8]. Another study in China focused on the link between the number of chemotherapy cycles and the survival rate of patients with bone-only metastasis[9]. Survival factors and prognostic factors of nasopharyngeal carcinoma patients were explored and analyzed, and the conclusion was drawn that the influencing factors of OS included the number of chemotherapy cycles and the number of metastatic sites. An investigation in Australia showed that the survival rate and pathological response rates of patients with muscle invasive bladder cancer were better in patients receiving 4 cycles of neoadjuvant

Table 5 Subgroup analysis of overall survival by Cox regression analysis of stage III gastric cancer patients

Variables	Death	Total	HR	95%CI	*P* value	*P* for interaction
Sex						0.639
Male	198	360	1.258	0.951-1.664	0.108	
Female	72	124	0.925	0.582-1.470	0.741	
Depth of tumor invasion						0.127
T3	43	123	1.044	0.569-1.916	0.888	
T4	227	361	1.207	0.929-1.567	0.158	
Number of positive lymph nodes						0.007
≤ 6	91	197	1.312	0.867-1.988	0.199	
≥ 7	179	287	1.115	0.832-1.496	0.466	
Vascular invasion						0.099
Negative	58	119	1.365	0.818-2.277	0.233	
Positive	211	365	1.138	0.868-1.492	0.350	
Neural invasion						0.059
Negative	73	159	1.389	0.872-2.211	0.166	
Positive	197	325	1.114	0.842-1.474	0.451	
Lauren classification						0.002
Intestinal	39	88	1.196	0.873-1.640	0.264	
Diffuse	168	254	1.184	0.872-1.606	0.280	
Mixed	63	142	0.975	0.760-1.250	0.840	
Maximum diameter of tumor in cm						< 0.001
< 6	108	230	1.071	0.734-1.563	0.722	
≥ 6	162	254	1.240	0.909-1.692	0.174	
Type of gastrectomy						0.004
Proximal	13	25	1.175	0.680-2.032	0.564	
Distal	65	142	0.915	0.560-1.494	0.722	
Total	192	317	1.125	0.976-1.297	0.105	

CI: Confidence interval; HR: Hazard ratio.

chemotherapy compared to patients receiving 3 cycles of neoadjuvant chemotherapy[10]. A study in China observed that the optimal number of adjuvant chemotherapy cycles for colon cancer patients is often less than 5[11].

While some studies have shown that more cycles of chemotherapy lead to a better prognosis, other studies have demonstrated no effect or a worsened effect. For example, patients with ovarian cancer receiving ≥ 5 chemotherapy cycles had a poorer prognosis than patients receiving 3-4 cycles[12]. Another study found that chemotherapy does not reduce survival in patients with inoperable stage III NSCLC. However, increased cycles (3 or more) led to more grade 3 toxicities[13]. In addition, a different study conducted on patients with ovarian cancer demonstrated that additional cycles did not affect the recurrence or complete pathologic response[14]. The 5-year survival rate of locally advanced rectal cancer treated with chemotherapy was higher than that of untreated patients[15]. Finally, patients with colorectal cancer who received adjuvant chemotherapy had a better 3-year survival rate than those who received shorter courses of chemotherapy[16].

Although it seems that increased chemotherapy cycles tend to achieve an oncologic benefit, the data is lacking for gastric cancer. Through a series of studies and analyses, the minimum number of cycles should be completed in gastric cancer patients to reduce the rate of tumor growth. During this process, the researchers found that patients who completed less than four cycles did not have a higher survival rate[17]. By analyzing the contents of previous studies, we can see that there is a certain correlation between gastric cancer recurrence and chemotherapy cycle. It was proved that > 9 cycles of che-

Table 6 Subgroup analysis of progression-free survival by Cox regression analysis of stage III gastric cancer patients

Variables	Death or recurrence	Total	HR	95%CI	*P* value	*P* for interaction
Sex						0.418
Male	227	360	0.925	0.712-1.200	0.555	
Female	88	124	0.555	0.363-0.846	0.006	
Depth of tumor invasion						0.266
T3	65	123	0.719	0.438-1.181	0.193	
T4	250	361	0.813	0.649-1.066	0.145	
Number of positive lymph nodes						0.170
≤ 6	108	197	0.933	0.640-1.361	0.719	
≥ 7	207	287	0.753	0.572-0.990	0.042	
Vascular invasion						0.382
Negative	72	119	0.824	0.518-1.311	0.414	
Positive	243	365	0.829	0.644-1.068	0.147	
Neural invasion						0.469
Negative	92	159	0.961	0.638-1.449	0.851	
Positive	223	325	0.773	0.593-1.007	0.056	
Lauren classification						0.083
Intestinal	47	88	0.886	0.498-1.576	0.632	
Diffuse	193	254	0.923	0.695-1.227	0.042	
Mixed	75	142	0.576	0.365-0.910	0.406	
Maximum diameter of tumor in cm						0.236
< 6	132	230	0.765	0.543-1.078	0.126	
≥ 6	183	254	0.850	0.636-1.136	0.271	
Type of gastrectomy						0.605
Proximal	15	25	0.781	0.282-2.162	0.635	
Distal	82	142	0.761	0.490-1.181	0.223	
Total	218	317	0.830	0.636-1.083	0.169	

CI: Confidence interval; HR: Hazard ratio.

motherapy could not reduce the recurrence rate of gastric cancer, and there was no advantage. Less than 9 cycles of chemotherapy increased the recurrence rate and reduced OS[18].

In the current study, the data demonstrated that ≥ 9 chemotherapy cycles did not confer any oncological benefit compared to < 9 chemotherapy cycles, indicating that ≥ 9 cycles may be considered overtreatment in stage II gastric cancer patients. Excessive chemotherapy may cause unpleasant side effects and impact the immune system, hepatic function, renal function, *etc*. However, ≥ 9 chemotherapy cycles did significantly reduce the probability of overall recurrence, local-regional metastasis, and distant metastasis rates in stage III gastric cancer patients but did not affect OS or PFS. Excessive chemotherapy cycles may have a psychological effect for patients (*i.e.* a patient may have less anxiety while being treated despite any side effects).

At present, there are some urgent problems in the research process. First of all, this study mainly conducted retrospective analysis and focused on a single factor. Although PSM was used to reduce the bias, it was still not accurate enough. The purpose of using PSM is to conduct a simulated randomized experiment. Secondly, the chemotherapy regimen is not standardized and complete; therefore, the effects of different chemotherapy regimens were not analyzed. Nonetheless, the interaction effect between chemotherapy cycles and Lauren classification, types of gastrectomy, and maximum diameter of the tumor on OS were determined for the first time.

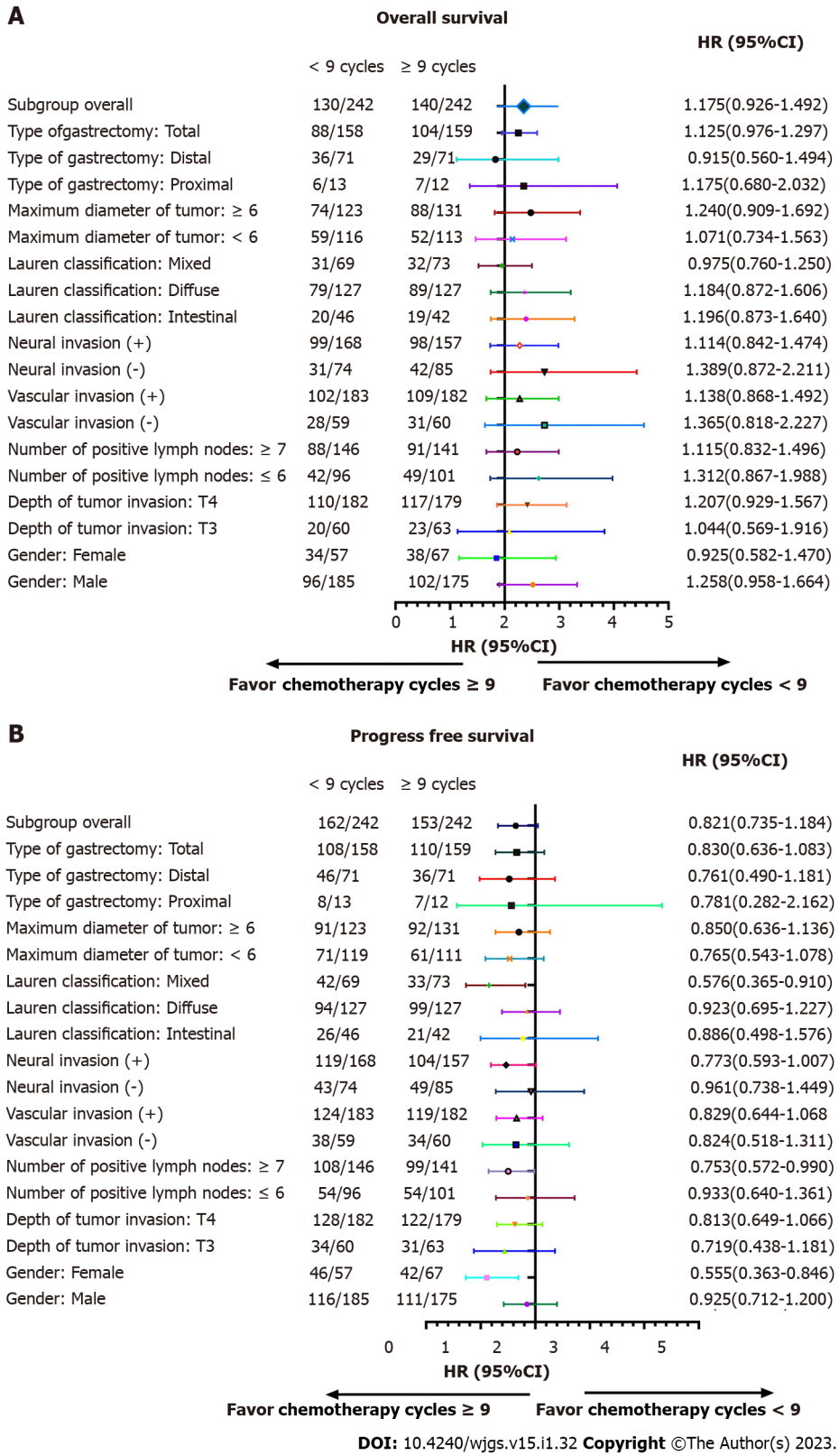

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Figure 5 Subgroup analysis of overall survival and progression-free survival for chemotherapy cycles in stage III gastric cancer patients.
A: Subgroup analyses of overall survival based on chemotherapy cycles; B: Subgroup analyses of progression-free survival based on chemotherapy cycles.

CONCLUSION

Overall, patients with stage II and III gastric cancer with chemotherapy cycles ≥ 9 have no significant effect on the prognosis of gastric cancer, so ≥ 9 cycles of chemotherapy are not adopted. However, in essence, ≥ 9 cycles of chemotherapy has a certain benefit in reducing the recurrence rate of stage III gastric cancer patients. Due to the lack of relevant data on gastric cancer and chemotherapy cycles at the

present stage, it is necessary to complete the chemotherapy regimen in a more standardized way, so as to deepen the research and finally clarify the correlation between the prognosis of gastric cancer and chemotherapy cycles.

ARTICLE HIGHLIGHTS

Research background

Several studies have shown an oncological benefit with increased cycles of chemotherapy in different cancer types. However, some studies have shown no effect or a worsened effect.

Research motivation

According to a series of exploration and analysis, it is found that there is no abundant data to prove the correlation between the prognosis of gastric cancer and the duration of chemotherapy.

Research objectives

The main purpose of this study is to analyze and explore whether there is a correlation between survival rate and chemotherapy cycle in patients with stage II gastric cancer and stage III gastric cancer.

Research methods

A 1:1 ratio was used in the propensity score matching analysis to reduce the differences between groups with different chemotherapy cycles. Progression-free survival, overall survival and recurrence were components of outcome indicators.

Research results

There was no statistically significant difference in progression-free survival and overall survival between the two groups of stage II and III patients. However, overall recurrence ($P < 0.001$), local-regional metastasis ($P = 0.002$), and distant metastasis ($P = 0.001$) in the ≥ 9 chemotherapy cycles group were significantly lower than those in the < 9 chemotherapy cycles group for stage III gastric cancer patients.

Research conclusions

For stage II and III gastric cancer patients, ≥ 9 cycles of chemotherapy should not be considered as far as possible, because ≥ 9 cycles of chemotherapy cannot effectively reduce the recurrence rate.

Research perspectives

After a series of studies, it is found that the relationship between the prognosis of gastric cancer and the chemotherapy cycle needs to be further explored to make a more abundant and standardized chemotherapy regimen.

FOOTNOTES

Author contributions: Li YF and Zhang WB conceptualized and designed the study, collected and analyzed the data, and wrote the manuscript; Li YF, Zhang WB and Gao YY revised the manuscript for important intellectual content; Gao YY participated in collection of the data; All authors approved the final version of the manuscript.

Institutional review board statement: This study was approved by the Institutional Research Ethics Board of Ethics Committee of Shanxi Cancer Hospital (Taiyuan, China) (No. 2022JC23) and followed the Declaration of Helsinki.

Informed consent statement: All the authors report having no relevant conflicts of interest for this article.

Conflict-of-interest statement: No additional data are available.

Data sharing statement: The authors have read the STROBE Statement - checklist of items, and the manuscript was prepared and revised according to the STROBE Statement - checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Development and validation of a novel nomogram for predicting overall survival in gastric cancer based on inflammatory markers

Pan-Quan Luo, En-Dong Song, Fei Liu, Abigail N Rankine, Li-Xiang Zhang, Zhi-Jian Wei, Wen-Xiu Han, A-Man Xu

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Abstract

BACKGROUND

Nearly 66% of occurrences of gastric cancer (GC), which has the second-highest death rate of all cancers, arise in developing countries. In several cancers, the predictive significance of inflammatory markers has been established.

AIM

To identify clinical characteristics and develop a specific nomogram to determine overall survival for GC patients.

METHODS

Nine hundred and four GC patients treated at the First Affiliated Hospital of Anhui Medical University between January 2010 and January 2013 were recruited. Prognostic risk variables were screened for Cox analysis. The C index, receiver operator characteristic (ROC) curve, and decision curve analysis were used to evaluate the nomogram.

RESULTS

Tumor node metastasis stage, carcinoembryonic antigen, systemic immune-inflammation index, and age were identified as independent predictive variables by multivariate analysis. Systemic immune-inflammation index value was superior to that of other inflammatory indicators. The ROC indicated the nomogram had a higher area under the curve than other factors, and its C-index for

assessing the validation and training groups of GC patients was extremely reliable.

CONCLUSION

We created a novel nomogram to forecast the prognosis of GC patients following curative gastrectomy based on blood markers and other characteristics. Both surgeons and patients can benefit significantly from this new scoring system.

Key Words: Gastric cancer; Nomogram; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Systemic immune-inflammation index

Core Tip: According to our study, the prognosis of patients with gastric cancer (GC) was significantly influenced by the systemic immune-inflammation index, carcinoembryonic antigen, tumor node metastasis stage, and age. We created a novel nomogram to predict the prognosis of GC patients following curative gastrectomy based on blood markers and other characteristics. Both surgeons and patients can benefit significantly from this new scoring system.

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INTRODUCTION

Nearly 66% of gastric cancer (GC) diagnoses, which has the second-highest death rate of all cancers[1], occur in developing countries[1,2]. The only curative treatment for patients is radical surgery, which increases the likelihood of a successful cure and lengthens patient survival. The high likelihood of cancer recurrence, however, means that the 5-year overall survival (OS) is still poor even after surgery [3]. The tumor node metastasis (TNM) stage is correlated with the prognosis of GC patients, but it is difficult to determine prior to surgery. Carcinoembryonic antigen (CEA) is one of the most utilized serum indicators in relation to stomach cancer according to recent research[4-6]. In order to diagnose cancer and predict recurrence following surgery, CEA has been employed[4]. The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are two additional blood indices that can be used to assess the prognosis of malignancy[5-7]. Additionally, the level of hemoglobin is related to a patient's prognosis[8]. The purpose of this study was to identify additional clinical blood indicators that may be used to evaluate GC patient prognosis and create a trustworthy scoring system.

There has been much research on the connection between cancers and inflammation. Cancer caused by inflammation has been shown to damage DNA and create microscopic metastases[9]. The body's immune system may become less effective, and tumor growth may be accelerated by the systemic inflammatory response. According to a related study, lymphocytes (LY), platelets (PLT), and neutrophils (NE) have a great impact on the systemic inflammatory response, which is linked to tumor formation[10,11]. The predictive usefulness of many systemic inflammation factors, such as NLR-PLR [12], PLT-NLR[13], and systemic immune-inflammation index (SII), has been well established in various malignancies[14,15]. There has not been any clinical research published comparing the prognostic significance of different scoring systems. In this study, we investigated additional clinical blood indicators and created a strong nomogram for predicting OS following gastrectomy.

MATERIALS AND METHODS

Patients

From January 2010 to January 2013, 904 GC patients were admitted to the First Affiliated Hospital of Anhui Medical University and provided blood samples and clinical data. All chosen participants were randomly divided into training (n = 543) and validation (n = 361) cohorts for the study's final analysis. Our hospital's Institutional Review Board and Ethical Committee approved this study.

Inclusion and exclusion criteria

The criteria for admission included: (1) A histological diagnosis indicated GC; (2) The malignancy was definitively and entirely removed after surgery; (3) All of the patients' peripheral blood tests were completed within 2 d after the operation; and (4) Multiple organ failure was not present. Patients were excluded if they met any of the following criteria: (1) They had other primary tumors; (2) They had undergone radiotherapy and chemotherapy prior to surgery; (3) They had any diseases that could interfere with peripheral blood cells, such as infections; and (4) They had passed away within 1 mo after operation. Finally, a cohort of 904 GC patients was examined.

Data collection and follow-up

Through the medical records department, information on the patient's age, sex, differentiation grade, tumor size, and other characteristics as well as clinical pathology was acquired. NE, LY, and PLT, *etc.* were obtained 3 d before the operation, and peripheral blood was analyzed. The CEA and hemoglobin cutoff values were obtained based on normal levels, and the median was used to determine the NE, LY, and PLT cutoff values. SII was calculated by PLT count × NE count/LY count. According to the ideal cutoff values, which were determined using the Youden index [maximum (sensitivity + specificity - 1)] [16], patients were divided into low and high groups. Patients were assigned to groups based on NLR–PLR as follows: (high NLR) + (high PLR) = 2; (only one high group) = 1; (low NLR) + (low PLR) = 0. The assignment of NLR-PLT was similar.

Statistical analysis

The categorical values were analyzed by the χ^2 test or the Fisher exact test, and continuous variables were analyzed by the Student's t test. The Cox appropriate hazard model was used to perform both multivariate and univariate survival analyses. In order to assess the accuracy of the prognostic model, the C-index and receiver operator characteristic (ROC) were utilized. R Studio and the SPSS program (version 19.0) were used for the full data analysis process.

RESULTS

ROC curve of SII, NLR, and PLR

By using the ROC curve of the greatest Youden index, we calculated the preoperative NLR, PLR, and SII value. Based on the Youden index, the optimal cutoff value of NLR, PLR, SII was calculated to be 2.0, 160.0, and 475.6, respectively.

Clinical characteristics of the training and validation groups

Table 1 showed the clinical data of the 904 GC patients (training group = 543, validation group = 361). The training group and validation group had no statistically significant differences ($P > 0.05$).

Univariate and multivariate analysis of the training cohort

Prognostic factors identified by univariate analysis were sex, hemoglobin, age, TNM, NLR, tumor size, PLR, SII, and CEA (Table 2). Multivariate analysis revealed that age, CEA, SII, and TNM were independent predictive factors for GC patients (Table 3).

The ROC curve of inflammatory markers

We used the ROC curve to compare the utility of all the inflammatory indicators in GC patients (Figure 1). The area under the curve (AUC) for SII was bigger than that of NLR, NLR-PLT, PLR, and NLR-PLR.

Nomogram for OS

A novel nomogram was created to predict the OS of GC based on the multivariate analysis result (Figure 2). Table 4 revealed the nomogram scoring method.

Validation of the nomogram model in the training group and validation groups

We applied calibration curves to verify the model in the training and validation groups (Figure 3). In the training group, the nomogram's C-index was 0.736, whereas in the validation group, it was 0.651. In order to further demonstrate the nomogram performance, we displayed the ROC of the nomogram (Figure 4). In addition, the AUC of the nomogram was large, showing that nomogram is dependable.

Decision curve analysis of the nomogram in the training and validation groups

Decision curve analysis results indicated the clinical use of the novel model for estimating 3-year and 5-year survival in GC patients in the training group and validation group (Figure 5).

Table 1 Baseline demographics and clinical characteristics of patients in the training and validation cohorts, *n* (%)

Variables	Training cohort (*n* = 543)	Validation cohort (*n* = 361)	*P* value
Pathological types			0.369
Adenocarcinoma	96 (91.3)	336 (93.1)	
Signet-ring cell	25 (4.6)	14 (3.9)	
Adenosquamous	1 (0.2)	2 (0.6)	
Squamous carcinoma	4 (0.7)	4 (1.1)	
Mucinous cell	17 (3.1)	5 (1.4)	
Macroscopic type			0.932
Borrmann I	22 (4.1)	15 (4.2)	
Borrmann II	391 (72.0)	260 (72.0)	
Borrmann III	113 (20.8)	72 (19.9)	
Borrmann IV	17 (3.1)	14 (3.9)	
Tumor location			0.415
Upper	250 (46.1)	156 (43.3)	
Middle	123 (22.7)	85 (23.6)	
Lower	169 (31.2)	119 (33.1)	
Surgery selection			0.344
Distal gastrectomy	117 (21.5)	88 (24.4)	
Total gastrectomy	401 (73.8)	261 (72.6)	
Proximal gastric resection	25 (4.6)	11 (3.0)	
Differentiated grade			0.662
High	25 (4.6)	16 (4.4)	
Middle	268 (49.5)	181 (50.2)	
Poor	248 (45.9.3)	164 (45.4)	
Sex			0.669
Male			
Female	142 (26.2)	89 (24.7)	
Age			0.925
< 60			
≥ 60	334 (61.5)	224 (62)	
Neutrophil count	3.17 ± 4.49	2.89 ± 4.06	0.326
Platelet count	196.5 ± 71.70	205.48 ± 84.35	0.086
Lymphocyte count	1.64 ± 1.68	1.58 ± 0.59	0.491

The Kaplan-Meier curves in training group

The training group was then separated into three subgroups depending on the cutoff value (< 60 was low risk; 60–120 was medium risk; > 120 was high risk). The Kaplan-Meier curve demonstrated the good outcomes (Figure 6).

DISCUSSION

The only curative form of treatment for GC is generally believed to be surgery. Early GC is typically difficult to diagnose due to the limitations of available procedures. The 5-year survival rate at the moment is quite poor. As a result, several researchers have worked to enhance the prognosis for GC patients. TNM stage and lymph node metastases were identified as important independent risk factors.

Table 2 Univariate analysis of the training cohort

Characteristics	β	HR (95%CI)	*P* value
Sex (male/female)	-0.305	0.737 (0.546, 0.995)	0.046
Age (< 60 / ≥ 60 yr)	0.333	1.395 (1.071, 1.818)	0.014
NLR (< 2 / ≥ 2)	0.406	1.502 (1.163, 1.940)	0.001
Tumor size (< 5 / ≥ 5 cm)	0.810	2.248 (1.746, 2.894)	< 0.001
TNM stage	1.062	2.892 (1.897, 4.409)	< 0.001
Histologic type	-0.788	0.455 (0.140, 1.478)	0.190
Neutrophil count	0.007	0.992 (0.963, 1.023)	0.622
Platelet count	0.001	0.999 (0.997, 1.000)	0.247
Lymphocyte count	0.048	1.049 (0.966, 1.139)	0.259
PLR (< 120/> 120)	0.482	1.619 (1.251, 2.096)	< 0.001
Pathological types	-0.614	0.541 (0.255, 1.148)	1.148
Macroscopic type	-0.114	0.893 (0.486, 1.640)	0.714
Tumor location	-0.102	0.903 (0.543, 1.502)	0.695
Surgery selection	0.098	0.903 (0.806, 1.508)	0.540
CEA (5 g/L)	1.238	3.449 (2.679, 4.440)	< 0.001
SII (< 475.6/ > 475.6)	0.632	1.881 (1.464, 2.417)	< 0.001
NLR-PLR	0.286	1.331 (1.194, 1.483)	< 0.001
NLR-PLT	0.269	1.308 (1.158, 1.477)	< 0.001
Hemoglobin	-0.350	0.705 (0.549, 0.905)	0.006

HR: Hazard ratio; TNM: Tumor node metastasis; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; CI: Confidence interval.

Table 3 Multivariate analysis of the training cohort

Characteristic	Beta	HR (95%CI)	*P* value
TNM	0.888	2.429 (1.588, 3.716)	< 0.001
CEA	0.839	2.313 (1.774, 3.015)	< 0.001
SII	0.405	1.499 (1.165, 1.930)	0.002
Age	0.303	1.354 (1.034, 1.771)	0.028

HR: Hazard ratio; TNM: Tumor node metastasis; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index; CI: Confidence interval.

However, because it is challenging to evaluate these prognostic factors prior to surgery, substantial research has been done recently on serum markers. This study, to the best of our knowledge, is the first to compare the serum score system and then create a novel nomogram that combines peripheral blood markers and clinical factors to predict OS at 1 year, 3 years, and 5 years.

The results demonstrated that age, SII, TNM stage, and CEA were each independent predictors of survival in GC patients. SII was a more effective indicator to predict OS based on the fact that its AUC was higher than that of NLR-PLR and NLR-PLT. The C-index of our newly constructed nomogram, which was based on independent prognostic variables, was 0.736, indicating that it is quite accurate in predicting GC patients' prognoses. This nomogram is an accurate score system because the decision curve analysis and calibration curve both supported its clinical use. Nomograms are more valuable than TNM stages for predicting prognosis in several cancers[17,18]. Since the nomogram's AUC in this study was higher than other elements, surgeons may use this scoring system to accurately assess a patient's prognosis and choose the most beneficial course of action in the clinic.

Table 4 Nomogram scoring system

SII	Points	Age	Points	CEA	Points	TNM	Points
1	0	1	0	1	0	I	0
2	26	2	20	2	55	II	58
						III	100

1: Low group; 2: High group; TNM: Tumor-Node-Metastasis; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

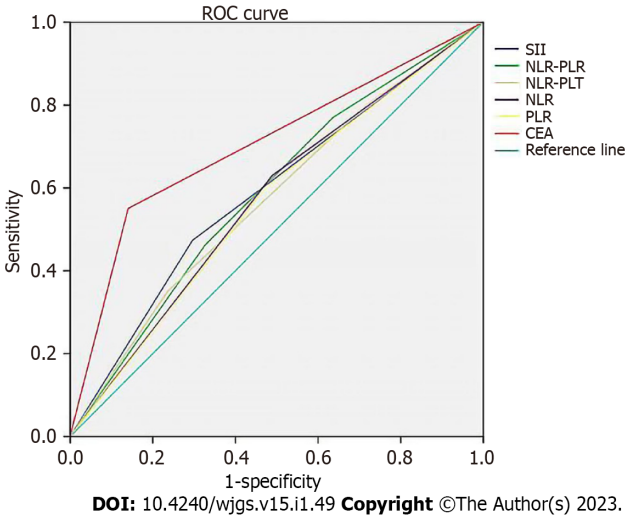

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Figure 1 The receiver operator characteristic curve of the blood markers. CEA: Carcinoembryonic antigen; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; ROC: Receiver operator characteristic; SII: Systemic immune-inflammation index.

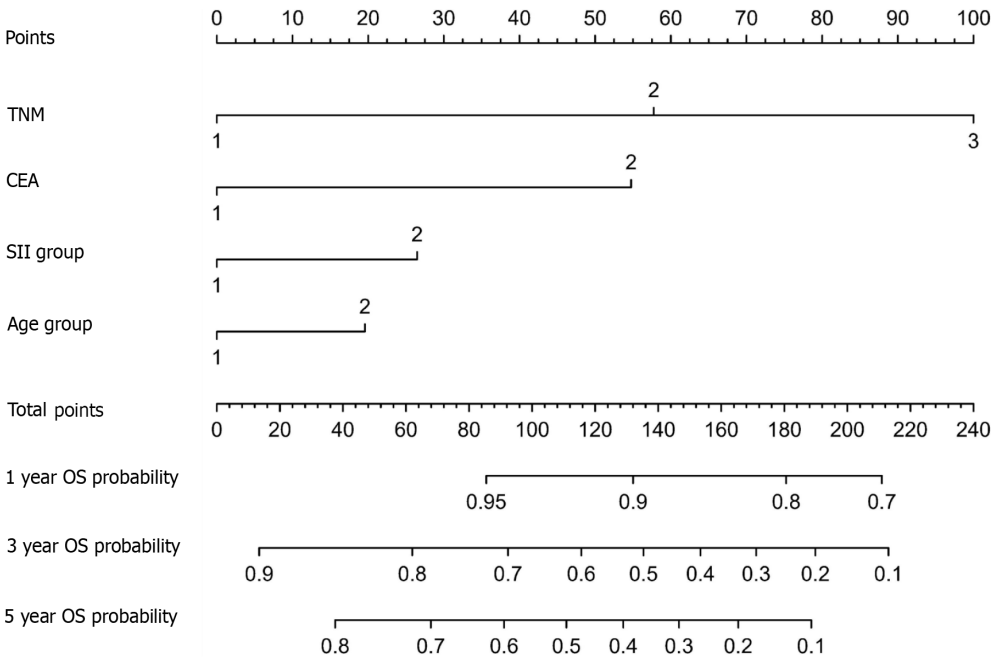

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Figure 2 Nomogram for predicting overall survival after curative resection of gastric cancer. CEA: Carcinoembryonic antigen; OS: Overall survival; SII: Systemic immune-inflammation index; TNM: Tumor node metastasis.

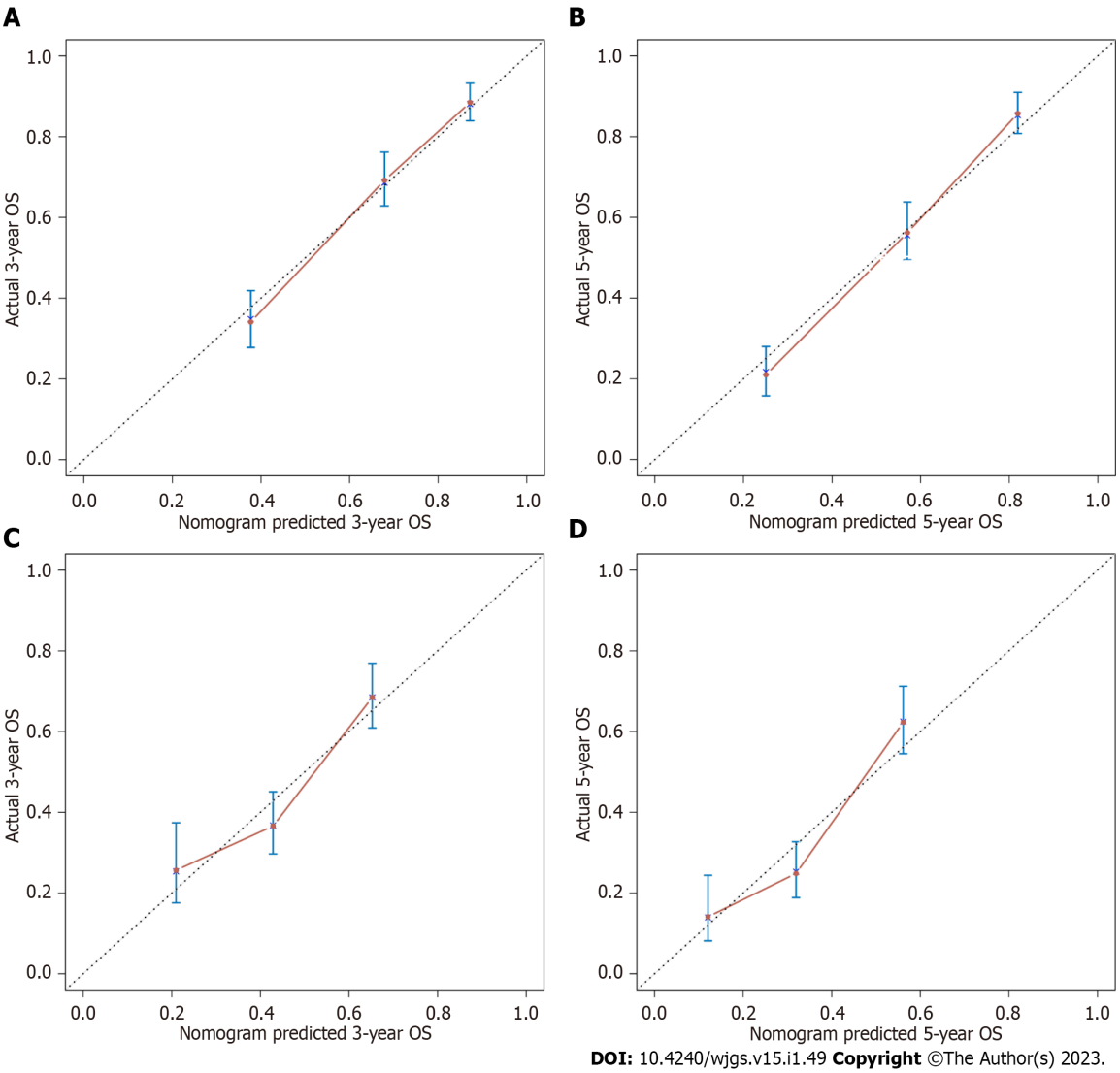

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Figure 3 Calibration curves. A: The prognostic nomogram for 3-year overall survival (OS) the training set; B: The prognostic nomogram for 5-year OS in the training set; C: The prognostic nomogram for 3-year OS in the validation set; D: The prognostic nomogram for 5-year OS in the validation set. OS: Overall survival.

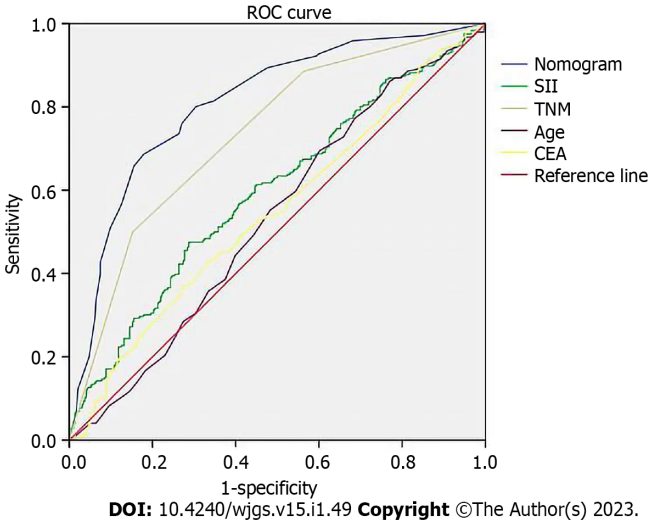

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Figure 4 The receiver operating characteristic curve of the prognostic nomogram in the training set. CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index; TNM: Tumor node metastasis; ROC: Receiver operator characteristic.

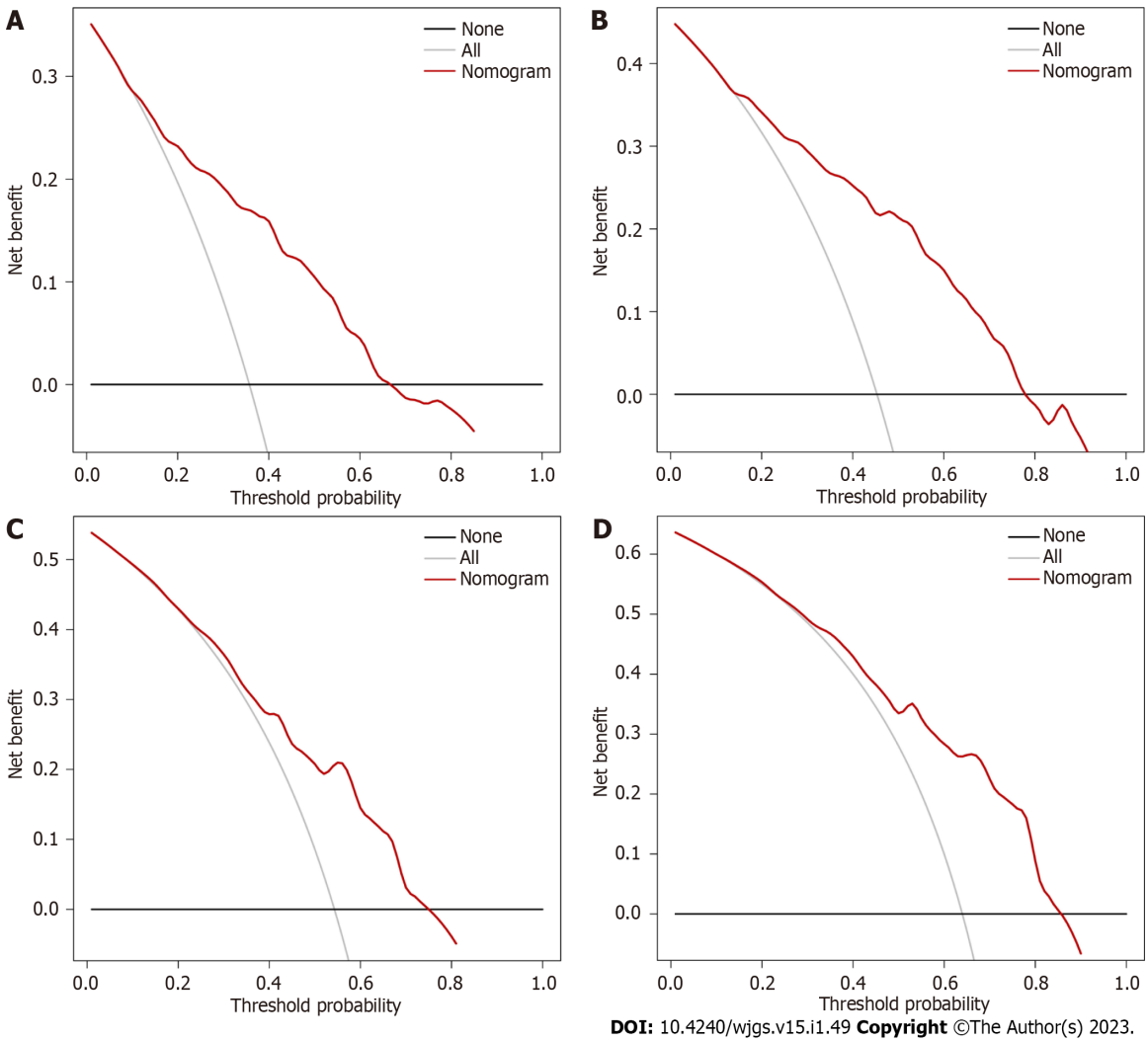

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Figure 5 Decision curve analysis. A: The decision curve analysis of the prognostic nomogram for predicting 3-year overall survival in the training set; B: The decision curve analysis of the prognostic nomogram for 5-year overall survival in the training set; C: The decision curve analysis of the prognostic nomogram for 3-year overall survival in the validation set; D: The decision curve analysis of the prognostic nomogram for 5-year overall survival in the validation set.

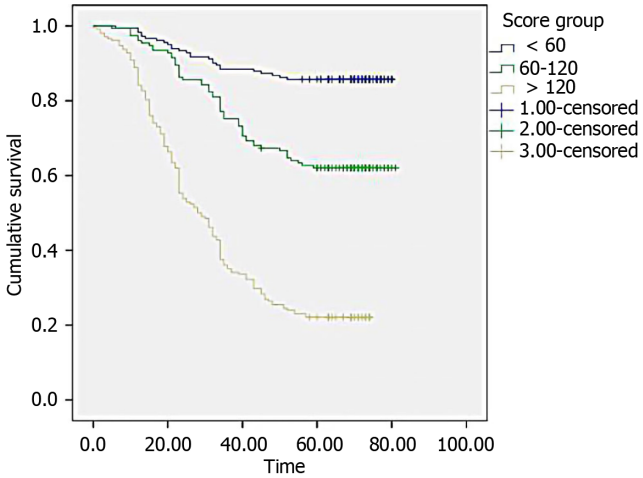

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Figure 6 Survival curves stratified by the score calculated by the nomogram in the training cohort (low risk: < 60; intermediate risk: 60–120; and high risk: > 120).

Four factors in our nomogram were significantly influenced by SII. According to recent studies, inflammation may have an impact on the development of cancer and long-term survival of patients[19]. SII, which may include NE count, PLT count, and LY count, was among them but was less frequently reported. NLR-PLT and NLR-PLR were associated with GC patient prognosis, whereas SII was an independent prognostic factor and had higher value. Our study proved that CEA was a reliable prognostic factor and that it may be used to screen for cancer recurrence. As a result, we need to pay more attention to patients who have elevated levels of CEA. Age was another important prognostic factor, and this result was consistent with earlier research[20]. With the increase of age, the immunity of elderly patients decreases significantly, which leads to recurrence and metastasis of cancer, thus elderly patients with GC typically have a worse outcome. As a result, these important factors need to be given more emphasis in order to improve patient outcomes, and the nomogram may be used more frequently in clinics.

CONCLUSION

In conclusion, our research showed that age, SII, TNM stage, and CEA were major predictive factors of the prognosis of GC patients, and the new nomogram was a valid prognostic tool for them.

ARTICLE HIGHLIGHTS

Research background

Nearly 66% of instances of gastric cancer (GC), which has the second-highest death rate of all cancers, occur in developing countries. The only curative treatment for patients is considered to be a radical surgery, which increases the likelihood of a successful cure and lengthens patient survival.

Research motivation

The high likelihood of cancer recurrence means that the 5-year overall survival (OS) is still poor even after surgery. The tumor node metastasis (TNM) stage is connected with the prognosis of GC patients, but it is difficult to determine prior to surgery.

Research objectives

To investigate more clinical characteristics and develop a specific nomogram to forecast OS for GC patients.

Research methods

Nine hundred and four GC patients treated at the First Affiliated Hospital of Anhui Medical University between January 2010 and January 2013 were recruited. Prognostic risk variables were screened using the Cox analysis. The C-index and receiver operator characteristic (ROC) curve were used to construct and evaluate the nomogram.

Research results

TNM stage, carcinoembryonic antigen, systemic immune-inflammation index, and age were identified as independent predictive variables by multivariate analysis. The systemic immune-inflammation index value was superior to that of other inflammatory indicators. The ROC indicated the nomogram had a higher area under the curve than other factors, and its C-index for assessing the validation and training groups of GC patients was extremely reliable.

Research conclusions

We created a novel nomogram to predict the prognosis of GC patients following curative gastrectomy based on the blood markers and other characteristics.

Research perspectives

Both surgeons and patients can benefit significantly from this new scoring system. The nomogram may be used more frequently in clinics.

FOOTNOTES

Author contributions: Luo PQ collected the clinical information of patients, performed the statistical analysis, and completed the writing of the manuscript; Song ED and Liu F participated in collecting the clinical information of patients and revising the statistical methods of the investigation; Luo PQ, Song ED, and Liu F contributed equally to

this work; Rankine AN helped perform the statistical analysis; Zhang LX, Wei ZJ, Han WX, and Xu AM designed the main study and critically revised the manuscript, and they contributed equally to this work; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

New perspectives on robotic pancreaticoduodenectomy: An analysis of the National Cancer Database

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Abstract

BACKGROUND

Pancreatic ductal adenocarcinoma is a common malignancy. Despite all advancements, the prognosis remains, poor with an overall 5-year survival of only 10.8%. Recently, a robotic platform has become an attractive tool for treating pancreatic cancer (PC). While recent studies indicated improved lymph node (LN) harvest during robotic pancreaticoduodenectomy (PD), data on long-term outcomes are insufficient.

AIM

To evaluate absolute LN harvest during PD. Secondary outcomes included evaluating the association between LN harvest and short- and long-term oncological outcomes for three different surgical approaches.

METHODS

We conducted an analysis of the National Cancer Database, including patients diagnosed with PC who underwent open, laparoscopic, or robotic PD in 2010-2018. One-way analysis of variance was used to compare continuous variables, chi-square test - for categorical. Overall survival was defined as the time between surgery and death. Median survival time was estimated with the Kaplan-Meier method, and groups were compared with the Wilcoxon test. A Cox proportional hazards model was used to assess the association of covariates with survival after controlling for patient characteristics and procedure type.

RESULTS

17169 patients were included, 8859 (52%) males; mean age 65; 14509 (85%) white. 13816 (80.5%) patients had an open PD, 2677 (15.6%) and 676 (3.9%) - laparoscopic

and robotic PD respectively. Mean comorbidity index (Charlson-Deyo Score) 0.50. On average, 18.84 LNs were harvested. Mean LN harvest during open, laparoscopic and robotic PD was 18.59, 19.65 and 20.70 respectively ($P < 0.001$). On average 2.49 LNs were positive for cancer and did not differ by the procedure type ($P = 0.26$). Vascular invasion was noted in 42.6% of LNs and did differ by the approach: 42.1% for open, 44.0% for laparoscopic and 47.2% for robotic PD ($P = 0.015$). Median survival for open PD was 26.1 mo, laparoscopic - 27.2 mo, robotic - 29.1 mo ($P = 0.064$). Survival was associated with higher LN harvest, while higher number of positive LNs was associated with higher mortality.

CONCLUSION

Our study suggests that robotic PD is associated with increased intraoperative LN harvest and has comparable short-term oncological outcomes and survival compared to open and laparoscopic approaches.

Key Words: Pancreatic cancer; Pancreaticoduodenectomy; Robotic surgery; National Cancer Database

Core Tip: This retrospective study evaluated absolute lymph node (LN) harvest during pancreaticoduodenectomy (PD) for analyzed over 17000 patients who underwent PD from 2010 to 2018. The number of LN harvested differed by the procedure type (open, laparoscopic, robotic), with the highest harvest obtained with the robotic approach. Procedure type was not associated with mortality or readmission rate within 30 d of hospital discharge. However, an increasing number of LN harvested was associated with survival, while a higher number of LN that were positive for cancer was associated with earlier mortality on multivariate analysis. Our study suggests that robotic PD has better LN harvest and is comparable to open and laparoscopic approaches for short-term oncological outcomes and survival.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the 11th most common malignancy diagnosed in the United States (US)[1]. The incidence of PDAC has increased over the past several decades; in 2022, it is estimated that there will be 62210 cases and 49830 deaths[2]. Late detection, early metastases, and resistance to therapy all contribute to its poor prognosis. Despite advancements in detection, surgical techniques, and widely adopted multidisciplinary care approaches, the prognosis remains poor with an overall 5-year survival of only 10.8%[1].

Surgery is the only potentially curative therapy for pancreatic cancer (PC), and pancreaticoduodenectomy (PD) is usually required to remove tumors in the head and neck of the pancreas. The very first resection of a periampullary tumor was performed in 1909, and the original technique of PD was described by Dr. Allen Oldfather Whipple in 1935[3]. The first laparoscopically assisted PD was done in 1994, and minimally invasive techniques evolved significantly in early 2000s, when Khachfe *et al*[4] performed the first robotic PD in 2001. Currently, it remains one of the most complex and technically challenging surgeries of the gastrointestinal system/alimentary tract. According to current literature, no major differences in outcomes result from different modifications of the PD procedure, including conventional, pylorus-preserving, or minimally invasive approaches. In addition, more extensive surgery including retroperitoneal lymphadenectomy, was studied in a prospective, single institution, randomized clinical trial, with comparable outcomes[5]. However, with the emergence of minimally invasive surgery the paradigm began to shift, and the utilization of laparoscopic and robotic PD approaches has recently increased and continues to gain in popularity.

Although the relatively new robotic PD approach offers equivalent or even slightly improved short-term perioperative outcomes with comparable rates of complications (pancreatic fistula and delayed gastric emptying), length of stay, and short-term oncologic outcomes (resection margins and mortality rates), the data regarding long-term oncologic outcomes are limited, as robotic PD gained ground only in the 2000s and is not universally accepted[6,7]. However, lymph node status is an important predictor

of recurrence and survival in surgically treatment of PC, and recent reports clearly demonstrated superior lymph node harvest using the robotic approach[8-10]. It is unclear if better lymph node harvest with robotic PD translates into improved outcomes in patients with PC.

We undertook the current study to compare open, laparoscopic, and robotic PD in terms of the absolute number of lymph nodes harvested. Secondary objectives included short-term oncological outcomes (*e.g.*, duration of hospital stay) as well as the association of lymph node yield with long-term oncologic outcomes.

MATERIALS AND METHODS

Institutional Assurances

Because we used only publicly available, anonymized data that preclude reidentifying of participants, our study was exempt from Institutional Review Board Review.

Patient identification and selection

We requested records from the National Cancer Database (NCDB) for patients with pancreatic adenocarcinoma diagnosed between 2004 and 2018. The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It includes more than 1500 cancer programs in the United States and Puerto Rico. Approximately 70% of newly diagnosed cancer cases in the United States are reported to the NCDB.

Patients with adenocarcinoma were identified with the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), using codes (C25. C25.0, C25.1, C25.3, C25.4, C25.7, C25.8, and C25.9).

Histological codes indicating adenocarcinoma (814: 8140/2 adenocarcinoma in situ; 8140/3 adenocarcinoma, not otherwise specified), duct carcinoma (850: 8500/2 intraductal adenocarcinoma noninfiltrating, not otherwise specified; 8500/3 invasive carcinoma of no special type) and other tumors of the head and neck of the pancreas that were treated with PD were also included. Tumors were classified as clinical stage I, II or III by the American Joint Committee on Cancer (AJCC, eighth edition).

We included all adult (age ≥ 18) patients who underwent PD based on site-specific coding in the database as well as type of procedure.

Exclusion criteria

We excluded procedures performed before 2010 because surgical approach was not consistently reported. Patients lacking documentation on surgical approach or diagnostic confirmation were similarly excluded. We did not include cases with the ICD-O-3 code C25.2 (Malignant neoplasm of tail of pancreas), tumors classified as clinical stage IV using the AJCC, 8th edition) cancer staging scale, and patients who had pancreatic surgery other than PD.

Variables of Interest

Covariates included patient characteristics (age, sex, race, comorbidities), tumor characteristics (grade, tumor size, clinical T classification, tumor location), treatment details (receipt and timing of chemotherapy, radiotherapy, hormone therapy, immunotherapy, and or type of surgery), and histopathology (pathologic T, pathologic N, nodal yield, lymph node ratio, margin status, lymph node vascular invasion). Secondary outcomes included length of stay, 30-d and 90-d mortality, 30-d readmission, and time to death. Patients who died in the hospital were excluded from analysis of length of stay and readmission.

Statistical analysis

Descriptive statistics were calculated for all covariates and outcomes. Continuous variables were compared across procedure type with one-way analysis of variance and categorical variables were compared with the chi-square test. Surgeries that started as laparoscopic or robotic and were converted to open were assigned to their original category.

Overall survival (OS) was defined as the time between surgery and death. Median survival time was estimated with the Kaplan-Meier method, and groups were compared with the Wilcoxon test. A Cox proportional hazards model was used to assess the association of covariates with survival after controlling for patient characteristics and procedure type. Observations were censored at the last follow-up if death was not observed. Variables that were significantly related to survival in bivariable analysis were candidates for the Cox model. The small number of tumors recorded as larger than 200 mm (n = 21, 0.12%) were recoded to 200 mm both to avoid undue influence in the multivariable model and because tumors of this size are rare and raise questions about the accuracy of reporting. Statistical significance was defined as $P < 0.05$. All statistical analysis was performed with Statistical Analysis Software (SAS) for Windows version 9.4 (SAS Institute, Inc., Cary, NC).

The statistical methods of this study were reviewed by Robin L Kruse and Chase Schlesselman.

RESULTS

Patient demographics

We included 17169 patients who underwent PD from 2010 to 2018 (Table 1). Most patients (13816, 80.5%) had an open procedure, 2677 (15.6%) had a laparoscopic procedure, and 676 (3.9%) underwent robotic surgery. Mean age at the time of surgery was 64.9 years [95%confidence interval (CI): 64.7-65.0], 8310 (48.4%) were females and 8859 were males (51.6%). Most (14509, 84.5%) patients identified themselves as white and 1739 (10.1%) as African American, with several groups too small to analyze separately that were included as "Other" (766, 4.5%). A smaller number (155, 0.90%) did not specify their racial identity. Hispanic ethnicity was indicated by 981 patients (5.7%). Mean comorbidity index (Charlson-Deyo Score) for the total cohort was 0.50 (95%CI: 0.49-0.51). Most patients (63.9%) had a score of 0, while 26.0% had a score of 1 and 10% of patients scored 2 or more (scores were capped at 3 in the database).

Tumor characteristics

Tumor characteristics are presented in Table 2. Adenocarcinoma was histologically confirmed in 7085 patients (41.3%), and in 6775 (39.5%) patients the final pathology was coded as ductal carcinoma, with both groups representing more than 80% of the cohort. The remainder (3309, 19.3%) had other malignant and benign histology codes. The overwhelming majority of the patients had pancreatic head lesions (15196, 88.5%) and the mean tumor size was 33.2mm (95%CI: 32.9-33.5). In the open PD group, 80.4% of patients were coded as AJCC clinical stage 1 or 2, compared with 78.7% and 68.5% in the laparoscopic and robotic groups, respectively.

Pancreatoduodenectomy evolution

Overall, the frequency of PD in the database increased from 1374 in 2010 to 2887 in 2018, with laparoscopic and robotic procedures representing a greater proportion of the total over time. While the majority of PD over the study period and in 2018 (76.4%) were still performed with an open approach, the increasing trend of minimally invasive techniques is readily apparent. The proportion of laparoscopic PD increased from 10.8% in 2010 to 16.5% in 2018 (Table 2). During the same period, the proportion of robotic-assisted PD increased from 1.0% to 7.1%. Even though the overall number of Whipple procedures more than doubled over this time, laparoscopic, and robotic PD in particular, remained rare operations at most facilities.

Lymph node harvest

Overall, an average of 18.8 (95%CI: 18.7-19.0) lymph nodes were harvested (Table 3). The number of lymph nodes harvested differed by surgical approach ($P < 0.0001$). Mean intraoperative lymph node harvest was 18.6 during open PD, 19.6 during laparoscopic procedures, and 20.7 with a robotic approach. Lymph nodes that were pathologically confirmed to have cancer cells averaged 2.49 for the entire cohort (95%CI: 2.44-2.55) and did not differ by procedure type ($P = 0.26$). Vascular invasion was noted in 42.6% (7313 patients) of pathologically examined lymph nodes. Vascular invasion differed by surgical approach, with 42.1% for open procedures, 44.0% for laparoscopic procedures, and 47.2% for robotic surgeries ($P = 0.015$).

Short-term oncological outcomes

Patients were characterized according to the pathological stage (Table 3), with 80.7% assigned to stages 0, 1, or 2. Overall, 13728 patients (80.0%) had R0 resection. In the open PD group, 79.9% of patients had R0 resection, compared with 80.3% and 79.3% with laparoscopic and robotic approaches, respectively ($P = 0.75$). There was no difference in the proportion of microscopic and macroscopic positive margins between groups. Patients spent an average of 10.7 d in the hospital. Robotic PD was associated with reduced length of stay after surgery (9.6 d) compared to open and laparoscopic approaches respectively (10.9 and 10.3 d, respectively; $P < 0.0001$). Prolonged hospital stay (≥ 10 d) was observed for 38.7% of patients in the open group, 33.6% of patients in the laparoscopic group, and 28.4% of those in the robotic group ($P < 0.0001$). Overall, 8.1% of patients had an unplanned readmission within 30 d of discharge; this did not differ between groups ($P = 0.71$). Following surgery, 30-d mortality was 2.7% and 90-d mortality was 5.3%. Mortality did not differ significantly between the groups.

Survival analysis

Median survival for patients who received open surgery was 26.1 mo (95%CI: 25.4-26.9). Patients who had laparoscopic surgery had a median survival of 27.2 mo (95%CI: 25.1-28.7), while those who had robotic procedures had a median survival of 29.1 mo (95%CI: 25.9-33.4). Survival did not differ by surgical approach ($P = 0.064$) (Figure 1). Several variables were associated with survival after surgery

Table 1 Demographic characteristics of adult patients who underwent pancreaticoduodenectomy, *n* (%)

Characteristic	Total (*n* = 17169)	Type of procedure			*P* value
		Open (*n* = 13816)	Laparoscopic[1] (*n* = 2677)	Robotic[2] (*n* = 676)	
Age, mean (95%CI)[3]	64.9 (64.7, 65.0)	64.81 (64.62, 64.99)	64.97 (64.55, 65.39)	65.36 (64.47, 66.25)	0.38
Sex					0.93
Female	8310 (48.4)	6694 (48.45)	1287 (48.08)	329 (48.67)	
Male	8859 (51.6)	7122 (51.55)	1390 (51.92)	347 (52.33)	
Race[4]					0.18
White	14509 (84.5)	11658 (84.38)	2284 (85.32)	567 (83.88)	
Black	1739 (10.1)	1435 (10.39)	237 (8.85)	67 (9.91)	
Other	766 (4.5)	597 (4.32)	133 (4.97)	36 (5.33)	
Unknown	155 (0.9)	126 (0.91)	23 (0.86)	6 (0.89)	
Hispanic ethnicity					0.009
Yes	981 (5.7)	809 (5.86)	145 (5.42)	27 (3.99)	
No	16188 (94.29)	13007 (94.14)	2532 (95.58)	649 (96.01)	
Charlson-Deyo score					0.52
0	10977 (63.9)	8867 (64.18)	1692 (63.21)	418 (61.83)	
1	4471 (26.0)	3578 (25.90)	710 (26.52)	183 (27.07)	
2	1134 (6.6)	904 (6.54)	175 (6.54)	55 (8.14)	
3 or more	587 (3.4)	467 (3.38)	100 (3.74)	20 (2.96)	
Surgical procedure					0.07
With partial gastrectomy	14068 (81.94)	11357 (82.20)	2152 (80.39)	559 (82.69)	
Without partial gastrectomy	3101 (18.06)	2459 (17.80)	525 (19.61)	117 (17.31)	

[1]Includes minimally invasive and minimally invasive converted to open.
[2]Includes robotic-assisted and robotic-assisted converted to open.
[3]Ages greater than 90 were recoded to 90.
[4]Includes patients who identified themselves as Korean, Filipino, Chinese, Japanese, Pakistani, Hawaiian, American Indian, Asian, or other smaller ethnic groups.

(Table 4). Greater age, tumor grades above 1, residual tumor at the surgical margins, pathological stages above 0, lower income quartiles, Charlson-Deyo scores above 0, larger tumor size, and longer times between diagnosis and surgery were all associated with earlier mortality. Compared with adenocarcinoma, duct carcinoma and other cancers were associated with delayed mortality, as was increasing year of diagnosis. Gender and surgical approach were not associated with survival. Of note, greater number of lymph nodes examined was associated with prolong survival while greater number of lymph nodes positive for cancer was associated with earlier mortality.

DISCUSSION

In our study of over 17000 patients who underwent PD from 2010 to 2018, we found that the number of lymph nodes harvested differed by procedure type (open, laparoscopic, robotic), but the number of lymph nodes that tested positive for cancer was not associated with type of procedure. After controlling for patient and tumor characteristics in a multivariable model, increasing number of lymph nodes harvested was associated with survival, while increasing number of lymph nodes that were positive for cancer was associated with earlier mortality. Procedure type was not associated with mortality or readmission within 30 d of hospital discharge.

Pancreatic surgery remains one of the most complicated and technically challenging surgical procedures due to the retroperitoneal location of the organ and its proximity to major vascular structures. With the known advantages of minimally invasive techniques and the potential of performing complex surgeries with enhanced precision and accuracy using robotic techniques, robotic

Table 2 Tumor characteristics for adult patients who underwent pancreaticoduodenectomy, *n* (%)

	Total (*n* = 17169)	Type of procedure			*P* value
		Open (*n* = 13816)	Laparoscopic[1] (*n* = 2677)	Robotic[2] (*n* = 676)	
Year of diagnosis					< 0.0001
2010	1374 (8.0)	1212 (8.77)	148 (5.53)	14 (2.07)	
2011	1514 (8.82)	1238 (8.96)	250 (9.34)	26 (3.85)	
2012	1601 (9.32)	1347 (9.75)	225 (8.40)	29 (4.29)	
2013	1738 (10.12)	1466 (10.61)	244 (9.11)	28 (4.14)	
2014	1816 (10.58)	1469 (10.63)	286 (10.68)	61 (9.02)	
2015	1986 (11.57)	1587 (11.49)	314 (11.73)	85 (12.57)	
2016	2154 (12.55)	1665 (12.05)	374 (13.97)	115 (17.01)	
2017	2099 (12.23)	1625 (11.67)	361 (13.49)	113 (16.72)	
2018	2887 (16.82)	2207 (15.97)	475 (17.74)	205 (30.33)	
Histology					< 0.0001
Adenocarcinoma	7085 (41.27)	5688 (41.17)	1177 (43.97)	220 (32.54)	
Duct carcinoma	6775 (39.46)	5482 (39.68)	1005 (37.54)	288 (42.60)	
Other	3309 (19.27)	2646 (19.15)	495 (18.49)	168 (24.85)	
Primary Site (C25.2 excluded)					< 0.0001
Head of pancreas	15196 (88.51)	12365 (89.50)	2253 (84.16)	578 (85.50)	
Body of pancreas	671 (3.91)	446 (3.23)	174 (6.50)	51 (7.54)	
Pancreatic duct	83 (0.48)	62 (0.45)	18 (0.67)	3 (0.44)	
Islet of Langerhans or endocrine pancreas	37 (0.22)	26 (0.19)	11 (0.41)	0	
Other/unspecified	11182 (6.88)	917 (6.64)	221 (8.26)	44 (6.51)	
AJCC Clinical Stage					0.0002
0	321 (1.87)	261 (1.89)	48 (1.79)	12 (1.78)	
1	230 (1.34)	202 (1.46)	21 (0.78)	7 (1.04)	
1A	1979 (11.53)	1593 (11.53)	297 (11.09)	89 (13.17)	
1B	4539 (26.44)	3715 (26.89)	703 (26.26)	121 (17.90)	
2	135 (0.79)	122 (0.88)	11 (0.41)	2 (0.30)	
2A	3320 (19.34)	2686 (19.44)	511 (19.09)	123 (18.20)	
2B	3154 (18.37)	2522 (18.25)	514 (19.20)	109 (16.12)	
3	612 (3.56)	507 (3.67)	97 (4.62)	8 (1.18)	
Unknown	2888 (16.82)	2208 (15.98)	475 (17.74)	205 (30.33)	
Grade					< 0.0001
Well differentiated	1993 (13.95)	1627 (14.01)	287 (13.03)	79 (16.77)	
2 – Moderately differentiated	6093 (42.66)	4903 (42.23)	990 (44.96)	200 (42.46)	
3 – Poorly differentiated	3976 (27.84)	3256 (28.05)	614 (27.88)	106 (22.51)	
4 - Undifferentiated	190 (1.33)	158 (1.36)	23 (1.04)	9 (1.91)	
Not determined	2030 (14.21)	1665 (14.34)	288 (13.08)	77 (16.35)	
Tumor size in mm, mean (95%CI)	33.21 (32.95, 33.48)	31.95 (30.69, 33.21)	33.13 (32.44, 33.82)	33.29 (33.00, 33.58)	0.015

[1]Includes minimally invasive and minimally invasive converted to open.
[2]Includes robotic-assisted and robotic-assisted converted to open. AJCC: American Joint Committee on Cancer.

Table 3 Lymph node harvest and short-term oncologic outcomes for patients who underwent pancreaticoduodenectomy, *n* (%)

Characteristic	Total (*n* = 17169)	Type of procedure			*P* value
		Open (*n* = 13816)	Laparoscopic[1] (*n* = 2677)	Robotic[2] (*n* = 676)	
Mean Lymph nodes harvested (95%CI)	18.84 (18.69, 18.98)	18.59 (18.43, 18.75)	19.65 (19.29, 20.02)	20.70 (19.89, 21.51)	< 0.0001
Mean Lymph nodes positive (95%CI)	2.49 (2.44, 2.55)	2.48 (2.48, 2.54)	2.58 (2.45, 2.72)	2.37 (2.11, 2.64)	0.26
Vascular invasion					0.0115
Yes	7313 (42.6)	5816 (42.1)	1178 (44.0)	319 (47.2)	
No	7764 (45.2)	6259 (45.3)	1208 (45.1)	297 (43.9)	
Unknown	2092 (12.2)	1741 (12.6)	291 (10.9)	60 (8.9)	
AJCC Pathological Stage					0.02
0	341 (1.99)	281 (2.03)	45 (1.68)	15 (2.22)	
1	79 (0.46)	68 (0.49)	9 (0.34)	2 (0.30)	
1A	995 (5.80)	778 (5.63)	169 (6.31)	48 (7.10)	
1B	1102 (6.42)	918 (6.64)	148 (5.53)	36 (5.33)	
2	45 (0.26)	44 (0.32)	1 (0.04)	0	
2A	2849 (16.59)	2322 (16.81)	435 (16.25)	92 (13.61)	
2B	8430 (49.10)	6826 (49.41)	1335 (49.87)	269 (39.79)	
3	317 (1.85)	262 (1.90)	47 (1.76)	8 (1.18)	
Unknown	3011 (17.54)	2317 (16.77)	488 (18.23)	206 (30.47)	
Surgical margins					0.75
No residual tumor (R0)	13728 (79.96)	11042 (79.92)	2150 (80.31)	536 (79.29)	
Microscopic residual tumor (R1)	3232 (18.82)	2601 (18.83)	495 (18.49)	136 (20.12)	
Macroscopic residual tumor (R2)	87 (0.51)	73 (0.53)	13 (0.49)	1 (0.15)	
Cannot be accessed	122 (0.71)	100 (0.72)	19 (0.71)	3 (0.44)	
Length of stay (95%CI)	10.77 (10.63, 10.90)	10.92 (10.77, 11.07)	10.29 (9.92, 10.66)	9.61 (8.97, 10.25)	< 0.0001
Readmission 30 d (readmitted)	1398 (8.14)	1113 (8.06)	227 (8.48)	58 (8.58)	0.71
Mortality 30 d (dead)	381 (2.67)	312 (2.69)	55 (2.50)	14 (2.99)	0.80
Mortality 90 d (dead)	752 (5.30)	634 (5.50)	97 (4.42)	21 (4.48)	0.09

[1]Includes minimally invasive and minimally invasive converted to open.
[2]Includes robotic-assisted and robotic-assisted converted to open. AJCC: American Joint Committee on Cancer.

PD has the potential to be a safe and feasible alternative to open and laparoscopic approaches. Data regarding long-term outcomes of robotic PD are lacking, however, as the technique is still developing and has not been universally integrated into routine surgical training and practice. In our work, we aimed to analyze PC data from the NCDB, because it represents a significant portion of newly diagnosed cancer cases nationwide and is considered one of the most comprehensive sources of cancer information in US[11].

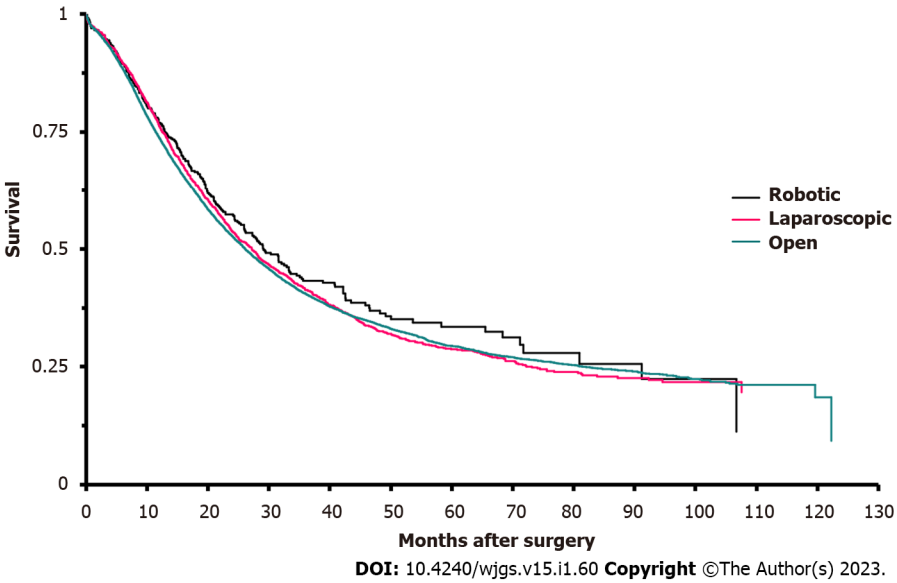
In our study, most (80.5%) of the surgeries were done using the open approach. Robotic PD was performed only in 3.9% of all PD cases. This highlights that robotic surgery has not been widely adopted; furthermore, the recently published Miami International Guideline on Minimally Invasive Pancreas Resection did not recommend a minimally invasive approach over open PD[12]. This is likely due to the limited number of training programs that have incorporated comprehensive training protocols for robotic pancreatic surgery in their curricula and the time needed to retrain established pancreatic surgeons on the robotic platform. Nonetheless, robotic outcomes continue to improve; recent data regarding outcomes of robotic PD have shown a significant decrease in postoperative mortality (from 6.7% to 1.8%) and comparable short-term outcomes with laparoscopic and open approaches[13-16]. Our study confirmed the overall trend of increased utilization of the robotic approach for PD, with an increase in prevalence from 1.0% to 7.1% over the study period.

Table 4 Cox proportional hazards model of mortality after surgery for patients with pancreatic cancer

Characteristic	Parameter estimate	Hazard ratio	95%CI	*P* value
Age (yr)	0.01621	1.02	1.01-1.02	< 0.0001
Male sex	0.02903	1.03	0.98-1.08	0.20
Race: White	ref			
Black	-0.0599	0.94	0.87-1.02	0.13
Other	-0.15749	0.85	0.76-0.96	0.009
Unknown	-0.16688	0.85	0.65-1.10	0.21
Hispanic ethnicity: No	ref			
Yes	-0.15238	0.86	0.78-0.95	0.0037
Unknown	-0.03096	0.97	0.82-1.15	0.72
Tumor grade: 1	ref			
2	0.45571	1.58	1.45-1.72	< 0.0001
3	0.70413	2.02	1.85-2.21	< 0.0001
4	0.80073	2.23	1.82-2.73	< 0.0001
Not determined, unknown	0.35723	1.43	1.28-1.60	< 0.0001
Surgical approach: Open	ref			
MIS, MIS to open	-0.0402	0.96	0.90-1.02	0.19
Robotic, robotic to open	0.00838	1.01	0.88-1.15	0.90
Surgical margins: No residual tumor	ref			
Macroscopic residual tumor	0.44741	1.56	1.19-2.05	0.0013
Microscopic residual tumor	0.34752	1.42	1.34-1.49	< 0.0001
Unknown, indeterminate	0.40122	1.49	1.15-1.94	0.0026
AJCC Pathological stage: 0	ref			
1/1A/1B	0.49238	1.64	1.22-2.18	0.0008
2/2A/2B	0.90708	2.48	1.86-3.29	< 0.0001
3	1.10653	3.02	2.21-4.14	< 0.0001
Census block median income quartile: > 63332				
$50354-$63332	0.06511	1.07	1.01-1.13	0.027
$40227-$50353	0.17171	1.19	1.12-1.26	< 0.0001
< $40227	0.19323	1.21	1.14-1.30	< 0.0001
Unknown	0.12115	1.13	0.61-2.10	0.70
Histology: Adenocarcinoma	ref			
Duct carcinoma	-0.05251	0.95	0.91-0.99	0.027
All others	-0.72939	0.48	0.44-0.52	< 0.0001
Charlson-Deyo score: 0				
1	0.10936	1.12	1.06-1.17	< 0.0001
2	0.18942	1.21	1.11-1.32	< 0.0001
3 or more	0.35643	1.43	1.26-1.62	< 0.0001
Lymph nodes examined	-0.01026	0.99	0.99-0.99	< 0.0001
Lymph nodes positive for cancer	0.05025	1.05	1.04-1.06	< 0.0001
Tumor size (mm)[1]	0.00479	1.01	1.00-1.01	< 0.0001
Year of diagnosis	-0.03434	0.97	0.96-0.98	< 0.0001

Weeks between diagnosis and surgery	0.00702	1.01	1.01-1.01	< 0.0001

[1]Tumors greater than 200 were recoded to 200.
MIS: Minimally invasive surgery; AJCC: American Joint Committee on Cancer.



DOI: 10.4240/wjgs.v15.i1.60 **Copyright** ©The Author(s) 2023.

Figure 1 Kaplan-Meier survival analysis of patients who underwent pancreaticoduodenectomy, by type of procedure received.

Lymph node status is an important indicator of survival in patients with PC, allows for proper staging, and aids in choosing the treatment strategies. Schwarz *et al*[17] postulated that both the lymph node ratio and the number of lymph nodes examined are important prognostic factors. They suggested that examining 15 total lymph nodes with curative-intent PD would optimize operative benefits. We report an average of 18.8 Lymph nodes examined overall, which is consistent with this guideline. Interestingly, a significantly higher percentage of lymph nodes had vascular invasion in the robotic group compared to the laparoscopic and open groups. The possibility that pathologists are more diligent at centers where robotic procedures are performed is raised by the increased presence of vascular invasion in the lymph nodes with metastatic disease found in robotic cases despite no difference in positive lymph nodes found between operative groups. If this were true, this may also explain the increased number of lymph nodes counted in robotic cases. On the other hand, the robotic approach is recognized to have more efficient retroperitoneal dissection of the celiac axis and superior mesenteric artery lymph nodes[9].

Short-term oncological outcomes including R0 resection, unplanned 30-d readmission, and 30- and 90-d mortality were comparable between the groups and are consistent with current literature[18,19]. Our study demonstrated that robotic PD is associated with reduced length of stay compared to open and laparoscopic approaches. This may affect psychological and psychosocial well-being for patients and should not be ignored.

Although survival analysis suggested that robotic PD is associated with a relatively longer median survival that than laparoscopic and open approaches, the difference was not statistically significant. However, our study provides new evidence on the comparable OS of patients undergoing robotic PD and warrants attention. This further supports the application of robotic techniques in the treatment of PC. However, additional prospective studies directly comparing minimally invasive and open PD approaches are needed to validate our findings and to further endorse utilization of the robotic surgical platform.

There are several potential limitations to this study. First, because surgical approach was not randomly assigned, there is potential for confounding. We used multivariable analysis to control for differences between groups, but it is possible that an important variable was not available to us. For example, the NCDB does not adequately characterize type of neoadjuvant therapy (chemotherapy *vs* chemoradiation) and it was excluded from the final analysis to avoid dropping too many cases. Secondly, the small number of institutions performing robotic PD may have unduly influenced the pathologic interpretations and tumor registry reporting. Third, NCDB does not include detailed operative reports, or types and rate of postoperative complications, precluding analysis of technical aspects or post operative complications. In addition, large national databases always carry inherent risk of coding errors and variation by staff at participating institutions. Moreover, AJCC clinical staging does

not contain an assessment for resectability using consensus guidelines, and surgical approach could have been chosen by radiographic staging of the tumor.

CONCLUSION

Our retrospective analysis of the NCBD demonstrated that robotic PD was both associated with increased number of lymph nodes harvested during surgery and equivalent to open and laparoscopic approaches with respect to rate of cancer positive lymph nodes, short-term oncological outcomes, and OS. This supports the continued incorporation of robotic PD into the surgical treatment of pancreatic neoplasms.

ARTICLE HIGHLIGHTS

Research background

Despite all advancements pancreatic ductal adenocarcinoma is still considered one of the deadliest types of cancer with an overall 5-year survival of only 10.8%. Pancreaticoduodenectomy (PD) is the only potentially curative approach for resectable pancreatic cancer (PC) and robotic PD has gain popularity in recent years.

Research motivation

Recent literature suggests that relatively new robotic PD approach offers comparable or even slightly improved short-term outcomes and equivalent rates of postoperative complications, however the data regarding long-term oncologic outcomes are limited. On the other hand, new studies demonstrated superior lymph node (LN) harvest using the robotic PD platform that could be an important predictor of recurrence and survival. Hence, we decided to analyze the National Cancer Database (NCDB) and compare open, laparoscopic and robotic PD in terms of absolute number of LN harvest and association of lymph node yield with long-term oncological outcomes.

Research objectives

The primary outcome was to evaluate absolute LN harvest during open, laparoscopic and robotic PD. Secondary outcomes included evaluating the association between LN harvest and short- and long-term oncological outcomes for three different surgical approaches, and more specifically - the association of LN harvest with overall survival (OS).

Research methods

Retrospective analysis of NCDB patients diagnosed with PC who underwent PD in 2010-2018. One-way analysis of variance was used for continuous variables, chi-square test - for categorical. OS was defined as the time between surgery and death. Median survival time was estimated with the Kaplan-Meier method, and groups were compared with the Wilcoxon test. A Cox proportional hazard model was used to access the association of covariates with survival after controlling for patient characteristics and procedure type.

Research results

17169 patients were included in the final analysis. 13816 (80.5%) patients had an open PD, 2677 (15.6%) and 676 (3.9%) - laparoscopic and robotic PD respectively. On average 18.84 LNs were harvested during PD. Mean LN harvest during open, laparoscopic and robotic PD was 18.59, 19.65 and 20.70 LNs respectively ($P < 0.001$). On average, 2.49 LNs were positive for cancer and did not differ by the procedure type ($P = 0.26$). Median survival for open PD was 26.1 mo, laparoscopic - 27.2 mo, robotic - 29.1 mo ($P = 0.064$). Survival was associated with higher number of positive LN harvest, while higher number of positive LNs was associated with higher mortality.

Research conclusions

Our study demonstrated that robotic PD was associated with increased number of lymph nodes harvested during surgery and equivalent to open and laparoscopic approaches with respect to short-term oncological outcomes and overall survival. This supports the continued incorporation of robotic PD into the surgical treatment of pancreatic neoplasms.

Research perspectives

Our study provides new evidence on superior LN harvest and comparable overall survival of patients undergoing robotic PD and warrants attention. Additional prospective studies directly comparing robotic and open approaches are needed to validate our findings and to further endorse utilization of

the robotic surgical platform.

FOOTNOTES

Author contributions: Kalabin A and Mani VR contributed to formulation of research goals and aims, development of study design, data accrual/interpretation, data analysis, original draft preparation, manuscript review and editing; Kruse RL contributed to data analysis, implementation of the statistical software/supportive algorithms, study validation/visualization, original draft preparation and editing; Schlesselman C contributed to data analysis, implementation of the statistical software/supporting algorithms, original draft preparation, manuscript review and editing; Li KY contributed to implementation of the statistical software/supporting algorithms, original draft preparation, manuscript review and editing; Staveley-O'Carroll KF contributed to management and coordination of the project, supervision of the research activity and execution, manuscript review and editing, critical review; Kimchi ET contributed to management and coordination of the project, supervision of the research activity and execution, manuscript review and editing, critical review; All authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Impact of body mass index in elderly patients treated with laparoscopic liver resection for hepatocellular carcinoma

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Abstract

BACKGROUND

The impact of obesity on surgical outcomes in elderly patients candidate for liver surgery is still debated.

AIM

To evaluate the impact of high body mass index (BMI) on perioperative and oncological outcome in elderly patients (> 70 years old) treated with laparoscopic liver resection for hepatocellular carcinoma (HCC).

METHODS

Retrospective multicenter study including 224 elderly patients (> 70 years old) operated by laparoscopy for HCC (196 with a BMI < 30 and 28 with BMI ≥ 30), observed from January 2009 to January 2019.

RESULTS

After propensity score matching, patients in two groups presented comparable results, in terms of operative time (median range: 200 min *vs* 205 min, $P = 0.7$ respectively in non-obese and obese patients), complications rate (22% *vs* 26%, $P = 1.0$), length of hospital stay (median range: 4.5 d *vs* 6.0 d, $P = 0.1$). There are no significant differences in terms of short- and long-term postoperative results.

CONCLUSION

The present study showed that BMI did not impact perioperative and oncologic outcomes in elderly patients treated by laparoscopic resection for HCC.

Key Words: Hepatocellular carcinoma; Body mass index; Laparoscopy; Surgical resection; Elderly patients; Propensity score matching

Core Tip: In order to evaluate the impact of a high body mass index (BMI) in elderly patients who underwent laparoscopic resection for hepatocellular carcinoma (HCC), we compared perioperative data and long-term outcomes from 10 European centers before and after propensity score matching. The present study showed that BMI did not impact perioperative and oncologic outcomes in elderly patients treated by laparoscopic resection for HCC.

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INTRODUCTION

Obesity is a significant contributing factor for the development of liver disease, starting from the stage of non-alcoholic steatohepatitis up to cirrhosis and hepatocellular carcinoma (HCC)[1-4]. Due to the constant increase of population aging, the treatment of HCC in elderly obese patient has become a global clinical issue[5]. Laparoscopic liver resection (LLR) provides the benefits of minimally invasive approach in terms of short-term outcomes[6,7], guaranteeing oncological results comparable to the open surgical approach[8,9]. However, data about the impact of obesity in patients undergoing LLR remain controversial, with some studies reporting higher body mass index (BMI) as a predictor of an adverse postoperative outcome[10] and other studies not reporting an increased risk of postoperative morbidity

linked to obesity[11]. The aim of this study was to evaluate the impact of BMI in elderly patients undergoing LLR for HCC, by comparing short- and long-term outcomes.

MATERIALS AND METHODS

This multicenter retrospective study included 224 patients treated between January 2009 and January 2019, at the following centers: Policlinico di Bari, Bari, Italy; Policlinico di Modena, Modena, Italy; Ospedale San Raffaele, Milan, Italy; Grande Ospedale Metropolitano Niguarda, Milan, Italy; Centre hé pato-biliaire Paul Brousse, Villejuif, France; Hôpitaux Universitaires Henri Mondor, Créteil, France; Hospital Universitario Sofía, Córdoba, Spain; Hôpitaux Universitaires de Genève, Geneva, Switzerland; Nouvel Hôpital Civil, Strasbourg, France; Centre Hospitalier Universitaire, Reims, France.

This study investigated patients resected for HCC demonstrating the following inclusion criteria: Child-Pugh class A and B disease; age ≥ 70 years; no evidence of major vessel branch invasion and no distant metastases. Based on the World HealthOrganization (WHO) definition of obesity (BMI > 30 kg/m^2)[12] patients were divided in two groups: BMI < 30 kg/m^2 group and BMI > 30 kg/m^2 group.

The diagnosis of HCC was done, according to the European Association for Study of Liver (EASL) consensus criteria[13], based on non-invasive findings or histopathology. The type of treatment was planned following multidisciplinary tumor board discussions.

LLR procedure

The surgical procedure was planned based on tumor features and liver function. Minor and major liver resections were performed according Brisbane classification[14]. The choice of position and the size of trocars depended by tumor location. Intraoperative ultrasonography represented a standardized initial step of surgical procedure. Liver parenchymal transection was performed with laparoscopic instruments using various energy devices such as the cavitation ultrasonic surgical aspirator ultrasonic, monopolar and bipolar forceps. The extent of resection depended on the size and anatomical location of the tumor and they were defined as "minor" for the resection of two or fewer Couinaud's liver segments, and 'major' for the resection ≥ 3 liver segments. The hepatic hilum was prepared for the Pringle's maneuver. The specimen was placed in an endocatch bag and removed from one of the trocars' incision sites.

Follow-up

Short-term outcomes after liver resection included the evaluation of the parameters in the perioperative period, including intraoperative variables such as operative time, and blood transfusion rate, and postoperative variables as complications rate (based on the Clavien-Dindo classification[15]), and length of hospitalization. Long-term outcomes included oncological results in terms of overall survival and disease-free survival (DFS). Liver blood tests were assessed on first, third and fifth postoperative day. Follow-up was performed once every 3 mo during the first year and every 4 mo thereafter with CT-scan and blood tests (including liver function and oncologic markers). Recurrence after treatment included repeat resection, locoregional treatment, till liver transplantation, or supportive care based on the patient's general status and liver disease according to the EASL-EORTC clinical practice guidelines[13].

Statistical analysis

Statistical analyses were carried out using the IBM SPSS Statistics 20 software. The *t*-test and Mann-Whitney *U* test were used to compare continuous variables. The chi-square test and Kruskal-Wallis test respectively was performed to compare categorical variables. The Kaplan-Meier method was used to assess recurrence-free survival (RFS) and overall survival (OS) curves. The Cox proportional hazard model was performed to analyse independent prognostic factors of longterm survival. A propensity score matching (PSM) analysis was performed to reduce selection bias obtaining two more homogeneous matched groups of patients in the resection and ablation groups. Variables included in our propensity model included age, comorbidities ≥ 2, American Society of Anesthesiologists (ASA) score, Child-Pugh and model for end-stage liver disease (MELD) scores, extent of resection, tumor number and size. A one-to-one PSM was performed with a caliper width of < 0.2 of the pooled standard deviation of estimated propensity scores, applying these variables to a logistic regression model and calculated C-statistics. A total of 27 out of the 196 patients in the BMI < 30 group and a total of 27 out of the 28 patients in the BMI > 30 group were matched for further analyses.

RESULTS

Before PSM

We included 224 patients treated with LLR for an HCC and aged ≥ 70 years. One hundred and ninty-six patients presented a BMI < 30 kg/m^2 and 28 patients presented a BMI > 30 kg/m^2. Demographic data

were similar between two groups, except for a higher rate of male in BMI ≥ 30 kg/m^2 group than in BMI < 30 kg/m^2 group (69% *vs* 93%, P = 0.001). Associated comorbidities were not increased in obese patients, as ASA and MELD score (Table 1).

Perioperative and postoperative data are described in Table 2. There were no significant differences in surgical time (median range: 200 min *vs* 220 min, P = 0.70, in the BMI < 30 and BMI > 30 respectively), rate of blood transfusion (16% *vs* 3%, P = 0.09), length of hospitalization (median range: 6.0 d *vs* 5.5 d, P = 0.20)

The global rate of postoperative complication was higher in the non-obese group (47% *vs* 25%, P = 0.02) compared to the obese group. Only the rate of wound infection was higher in the obese group (11% *vs* 2%, P = 0.04).

The 90-d mortality rate didn't present significative difference between the two groups (5% in BMI < 30 group and 0% in BMI > 30 group, P = 0.60). The estimated 1- and 3-year OS rates were 100% and 92.3% in BMI > 30 group, and 96% and 91.4% in BMI < 30 group (P = 0.004; Figure 1A) respectively. The estimated 1- and 3-year DFS rates were 96% and 67% in BMI > 30 group, and 82% and 36% in BMI < 30 group (P = 0.50; Figure 1B) respectively.

After PSM

After matching, we obtained a more homogeneous population for both groups (Table 1). The variables included in the PSM were age, comorbidities, ASA and MELD score, Child Pugh score, tumor size, tumor number and extent of resection. Peri-operative and post-operative results are analytically described in Table 2. The post-operative follow up didn't reveal any difference in the complication's rate between BMI > 30 and BMI < 30 group (26% *vs* 22%, P = 1.0), nor in grade of severity (Clavien-Dindo grades III-IV) (4% *vs* 7% P = 0.6). Moreover, operative time (median range: 205 min *vs* 200 min, P = 0.7) and rate of blood transfusion (3% *vs* 18%, P = 0.2) were similar. The estimated 1- and 3-year overall survival rates were 100% and 92.3% in the BMI > 30 group, and 88.4% and 83.5% in the BMI < 30 group (P = 0.2; Figure 1C).

The estimated 1- and 3-year DFS rates were 96.2% and 65.8% in the BMI > 30 group, and 87.5% and 86.2% in the BMI < 30 group (P = 0.5; Figure 1D) respectively.

DISCUSSION

The impact of obesity on surgical results in elderly patients who underwent liver resections remains a subject of vivid debate. An increased surgical risk has been expected because of comorbidities, associated to obesity and old age, underlying liver disease and technical difficulties[16-20]. Our multicenter study did not confirm this hypothesis and showed that LLR can be safely performed in treatment of HCC also in elderly patients with a BMI ≥ 30 kg/m^2. The evaluation of the influence of BMI in elderly population is important because of the increasing prevalence of this condition associated to an higher average life expectancy[21,22].

The increasing BMI has been reported as a predisposition to develop various diseases, including diabetes mellitus, hypertension, respiratory disease and certain type of cancers[23-25]. Our data did not show differences in term of rate of comorbidities or tumor characteristics, even after PMS analysis, according to various preoperative parameters (age, comorbidities, ASA and MELD score, Child Pugh score, tumor size, and tumor number and extent of resection), which resulted in a more homogeneous and therefore comparable population.

Even though the initial hypothesis that obesity negatively affected the outcomes of minimally invasive approach was not verified[26], data regarding LLR in obese patients were controversial. After the evaluation of surgical procedures ended with Second International Consensus Conference on LLR [27], a scoring system was built to stratify LLR into groups with increasing degree of difficulty[28]. This IWATE score aimed to preoperatively predict, the technical difficulty of various LLR, but without including body habitus. So, the question whether anthropometric variables really have an impact on perioperative outcomes, remains.

Using operative time, rate of blood transfusion and rate of conversion as surrogates of surgical difficulty, Ome *et al*[29] reported significantly longer median operation time in obese compared to non-obese patients, while for Uchida *et al*[30] BMI was an independent predictor of longer operative time > 200 min. Lee *et al*[31] reported a significant difference in operative time and incidence of blood transfusion in overweight compared to normal weight patients, but no difference for obese patients. In accordance to the abovementioned data, the results of this study also suggest similar rate of blood transfusion and operative time in patients with BMI < 30 kg/m^2 and those with BMI ≥ 30 kg/m^2.

The advantages of a minimally invasive approach in liver surgery, including lower abdominal wall morbidity and early postoperative rehabilitation[32,33], may be more beneficial for the subgroup of obese patients. A recent systematic review[34] reported similar rates of postoperative complications between obese and non-obese patients, although several issues including discrepancy in the obesity definition, limit the validity of these results. Nomi *et al*[35] reported that the postoperative course of obese patients was not negatively affected by a higher incidence of infectious complications nor liver

Table 1 Preoperative and clinical characteristics of elderly patients with hepatocellular carcinoma with a body mass index < 30 or ≥ 30 who underwent laparoscopic liver resection

	LLR before PSM (224)			After PSM (54)		
	BMI < 30 (196)	BMI ≥ 30 (28)	*P*	BMI < 30 (27)	BMI ≥ 30 (27)	*P*
MALE	135 (69)	26 (93)	0.00	17	25	0.02
Age (yr), median (range)	75.2 (69.5-90.0)	75.3 (69.7-86.6)	0.70	76.3 (70.6-81.2)	73.1 (70-82.3)	0.70
BMI (kg/cm²), median (range)	26.7 (19.0-29.0)	32.5 (30.0-52.0)	0.00	26.7 (25.0-267.0)	33 (30-37)	
Co-morbidities > 2, *n* (%)	77 (80)	9 (32)	0.50	14	9	0.27
Cause of Cirrhosis, *n* (%)						
Hepatitis C virus	102 (52)	12 (43)	0.40	16	11	0.27
Hepatitis B virus	39 (20)	4 (14)	0.60	7	4	0.50
Alcohol	23 (12)	7 (25)	0.07	1	7	0.05
Others	32 (16)	5 (18)	0.80	3	5	0.70
ASA score, *n* (%)			0.80			1.00
I-II	84 (43)	11 (39)		10	10	
III-IV	112 (57)	17 (61)		17	17	
Blood tests median (range)						
Bilirubin (mg/dL)	0.9 (0.2-4.2)	0.9 (0.2-2.1)	0.8	0.9 (0.3-1.1)	0.5 (0.2-1.1)	0.70
Creatinine (mg/dL)	0.9 (0.2-2.5)	0.9 (0.4-1.9)	1.00	0.9 (0.8-1.5)	0.9 (0.7-2)	0.80
Platelet count, × 10^9/L	176 (45-421)	187 (72-468)	0.3	144 (47-337)	168 (117-396)	0.80
INR	1.1 (0.6-2.0)	1.08 (0.7-1.67)	0.3	1.1 (1-1.5)	1 (1-1.3)	0.50
CHILD-PUGH, *n* (%)			0.2			1.00
A	177 (90)	23 (82)		23	22	
B	19 (68)	5 (18)		4	5	
MELD median (range)	6 (6-16)	6 (6-13)	0.6	8 (6-12.5)	8 (6-13)	0.40
Tumors number *n* (%)			0.06			1.00
Single nodule	191 (97)	25 (89)		24	24	
Multi nodules	5 (3)	3 (11)		3	3	
Tumors size (mm), median (range)	30 (9-50)	30 (18-50)	0.6	30 (9-50)	27 (24-35)	0.30
Bilobar tumor, *n* (%)	1 (0.5)	1 (3)	0.2	1	1	1.00
Tumor in PS segment, *n* (%)	41 (21)	6 (21)	1.00	5	5	1.00
Histologically proven *n* (%)	31 (16)	8 (29)	0.11			
Previous treatment, *n* (%)	12 (6)	3 (10)	0.4			
Major hepatectomy, *n* (%)	22 (11)	2 (7)	0.7	1	2	1.00
Operative time > 240 min	73 (37)	12 (43)	0.7	150 (80-210)	150 (65-155)	0.70

Continuous variables were compared using an independent sample *t*-test and Mann-Whitney *U* test. Categorical variables were compared using the chi-square test and Kruskal-Wallis test respectively. LLR: Laparoscopic liver resection; PSM: Propensity score matching; HCC: Hepatocellular carcinoma; BMI: Body mass index; ASA: American Society of Anesthesiologists; MELD: Model for End Stage Liver Disease.

specific complications. Yu *et al*[36] reported a higher rate of bile leak in obese compared to non-obese patients. The herein presented data demonstrate a similar postoperative outcome, with no significant differences in major complications (Clavien Dindo III-IV) nor liver related complications in obese compared to non-obese patients.

View magnification of, optimal exposure with liver mobilization and the increase of dedicated tools allow a clearer visualization of deep structures, small vessels and biliary ducts[7,36,37]. The authors speculate this "power" of laparoscopy can justify a lower rate of postoperative complications not only in

Table 2 Preoperative and clinical characteristics of elderly patients with hepatocellular carcinoma with a 30 > body mass index ≥ 30 who underwent laparoscopic liver resection

	LLR before PSM (224)			After PSM (54)		
	BMI < 30 (196)	BMI ≥ 30 (28)	*P*	BMI < 30 (27)	BMI ≥ 30 (27)	*P*
Operative time (min), median (range)	200 (70-600)	220 (65-337)	0.70	200 (80-320)	205 (65-337)	0.7
Blood transfusion, *n* (%)	32 (16)	1 (3)	0.09	5 (18)	1 (3)	0.2
Dindo-Clavien classification, *n* (%)			0.23			0.6
I-II	18 (92)	27 (97)		23 (93)	26 (96)	
III-IV	16 (8)	1 (3)		2 (7)	1 (4)	
Postoperative complications, *n* (%)			0.02			1.0
Yes	93 (47)	7 (25)		6 (22)	7 (26)	
No	103 (53)	21 (75)		21 (78)	20 (74)	
Type of complication, *n* (%)						
Liver failure	15 (8)	1 (3)	0.70	2 (7)	1 (4)	1.0
Ascites	24 (12)	2 (7)	0.70	3 (11)	2 (7)	1.0
Biliary leakage	2 (1)	1 (3)	0.30	0	1 (4)	1.0
Hemorrhage	8 (4)	0	0.60	2 (7)	0	0.5
Systemic infection	14 (7)	1 (3)	0.70	2 (7)	1 (4)	1.0
Intra-abdominal abscess	7 (3)	0	0.60	2 (7)	1 (4)	1.0
Wound infection	4 (2)	3 (11)	0.04	0	3 (11)	0.2
Portal thrombosis	2 (1)	0	1.00	1 (4)	0	1.0
Pulmonary	15 (7)	0	0.20	2 (7)	0	0.5
Cardiac	11 (5)	1 (3)	1.00	2 (7)	1 (4)	1.0
Renal	8 (4)	0	0.60	2 (7)	0	0.5
Reoperation, *n* (%)	6 (6)	1 (3)	1.00	0	1 (4)	1.0
Postoperative death, *n* (%)	7 (3)	0	0.60	2 (7)	0	0.5
Postoperative treatment, *n* (%)	6 (3)	1 (3)	1.00	0	1 (4)	1.0
Length of hospital stay, median (range)	6 (2-40)	5.5 (3-21)	0.20	4.5 (2-40)	6 (3-21)	0.1
Mortality at 90 d, *n* (%)	9 (5)	0	0.60	2 (7)	0	0.5

Continuous variables were compared using an independent sample *t*-test and Mann-Whitney *U* test. Categorical variables were compared using the chi-square test and Kruskal-Wallis test respectively; LLR: Laparoscopic liver resection; PSM: Propensity score matching; BMI: Body mass index.

terms of preservation of abdominal wall integrity, linked with prevention on respiratory diseases and reduction of postoperative pain, but also with a greater accuracy in resection technique, especially in the hands of experienced surgeons.

Oncological outcomes following PSM were also similar, as no differences were noted in disease-free and overall survival in obese *vs* non-obese patients, undergoing LLR for HCC. This is also in accordance with in the majority of published data[34]. These results suggest that also elderly obese patients can benefit from surgical treatment in terms of long-term outcomes, mainly driven by the excellent short-term outcome of laparoscopy.

CONCLUSION

In conclusion, according to the present study, BMI does not impact surgical outcomes of LLR in elderly patients treated for HCC. Thorough patient selection, based on liver volume and function evaluation, as well as patient habitus and comorbidities, could result in safe and feasible LLR in elderly obese patients.

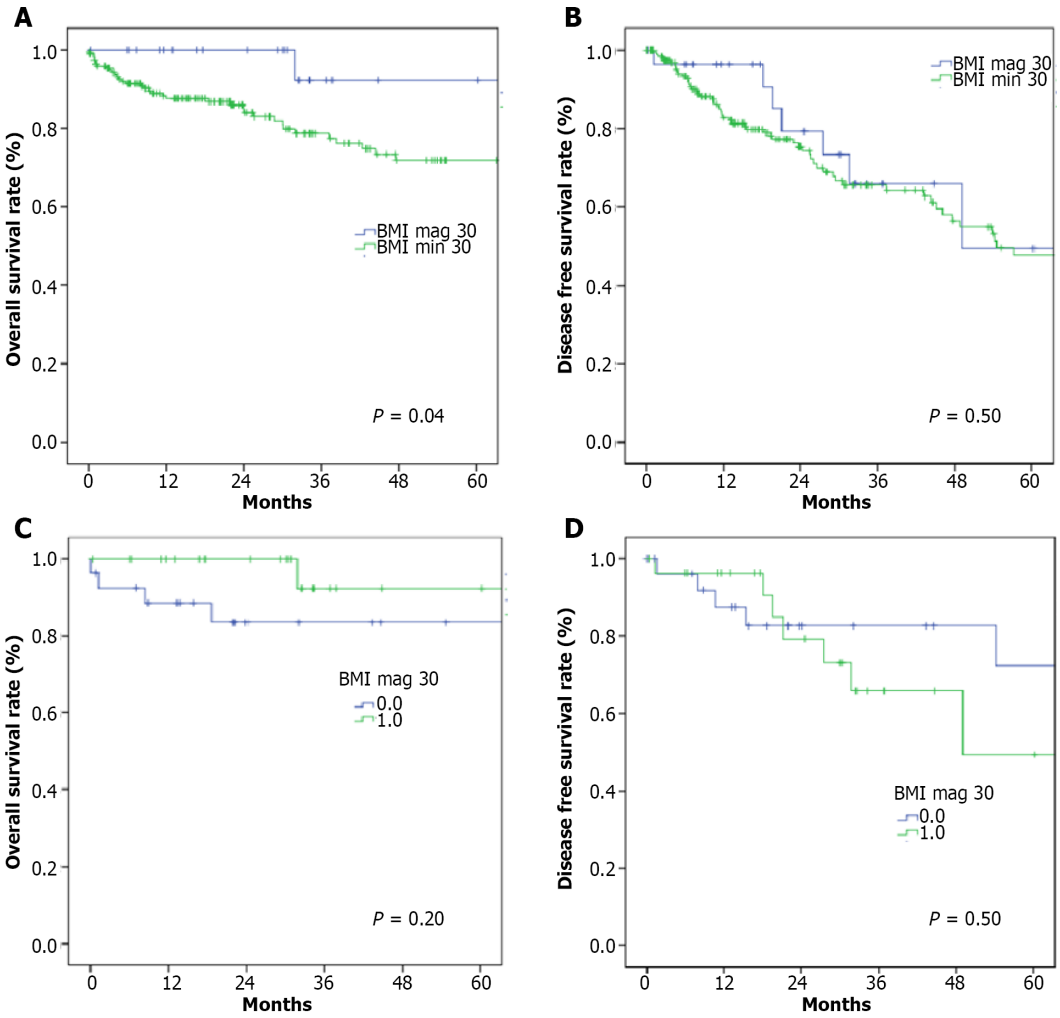

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Figure 1 Survival curves and Tumor recurrence curves (Kaplan-Meier method) of elderly patients with hepatocellular carcinoma with a 30 > body mass index ≥ 30 who underwent laparoscopic liver resection before propensity score matching. A: Overall survival (OS) curves were constructed using the Kaplan-Meier method and compared using the log-rank test, OS significantly did not differ between the two groups; B: Recurrence-free survival (RFS) curves were constructed using the Kaplan-Meier method and compared using the log-rank test, hepatocellular carcinoma recurrence significantly differs between the two groups; C: OS curves were constructed using the Kaplan-Meier method and compared using the log-rank test; after propensity score matching, survival remained significantly different; D: RFS curves were constructed using the Kaplan-Meier method and compared using the log-rank test; after propensity score matching, recurrence remained significantly different. BMI: Body mass index.

ARTICLE HIGHLIGHTS

Research background

A high body mass index (BMI) could represent a factor which impacts perioperative outcomes in elderly patients who underwent laparoscopic liver resection (LLR).

Research motivation

To evaluate of postoperative outcomes between elderly (age > 70 years) patients with a BMI ≥ 30 and BMI < 30 who underwent a LLR for hepatocellular carcinoma (HCC).

Research objectives

The analysis of short (perioperative) and long-term (oncological results) outcomes.

Research methods

The analysis of data was performed before and after propensity score matching.

Research results

After propensity score matching, patients in two groups presented comparable results, in terms of operative time complications rate length of hospital stay. There are no significant differences in terms of

short- and long-term postoperative results.

Research conclusions

The present study showed that BMI did not impact perioperative and oncologic outcomes in elderly patients treated by laparoscopic resection for HCC.

Research perspectives

Randomized controlled studies are needed to better explore these results.

FOOTNOTES

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Institutional review board statement: This study didn't require the approval by the Ethics Committee of the Azienda Ospedaliera Universitaria Policlinico of Bari, General Regional Hospital "F. Miulli", Acquaviva delle Fonti (BA), San Raffaele Hospital of Milan, Gustave Roussy Cancer Campus Grand Paris of Paris, Hospital University Reina Sofía of Córdoba, Centre hospitalier universitaire Henri Mondor of Paris, Geneva University Hospitals and Medical School of Geneva, University of Modena and Reggio Emilia of Modena, Institut de Recherche Contre les Cancers de l'Appareil Digestif (IRCAD) of Strasbourg, Hôpital Robert Debré of Reims, Niguarda Hospital of Milan, Centre Hepatobiliaire, Hopital Paul Brousse, of Paris.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors are aware of the content of the manuscript and have no conflict of interest.

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ORIGINAL ARTICLE

Retrospective Study

Effects of postoperative use of proton pump inhibitors on gastrointestinal bleeding after endoscopic variceal treatment during hospitalization

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Abstract

BACKGROUND

Endoscopic variceal treatment (EVT) is recommended as the mainstay choice for the management of high-risk gastroesophageal varices and acute variceal bleeding in liver cirrhosis. Proton pump inhibitors (PPIs) are widely used for various gastric acid-related diseases. However, the effects of PPIs on the development of post-EVT complications, especially gastrointestinal bleeding (GIB), remain controversial.

AIM

To evaluate the effects of postoperative use of PPIs on post-EVT complications in patients with liver cirrhosis during hospitalization.

METHODS

Patients with a diagnosis of liver cirrhosis who were admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command, treated by an attending physician between January 2016 and June 2020 and underwent EVT during their hospitalization were included. Logistic regression analyses were performed to explore the effects of postoperative use of PPIs on the development of post-EVT complications during hospitalization. Odds ratios (ORs)

with 95% confidence intervals (CIs) were calculated.

RESULTS

A total of 143 patients were included. The incidence of post-EVT GIB and other post-EVT complications was 4.90% and 46.85%, respectively. In the overall analyses, postoperative use of PPIs did not significantly reduce the risk of post-EVT GIB (OR = 0.525, 95%CI = 0.113-2.438, *P* = 0.411) or other post-EVT complications (OR = 0.804, 95%CI = 0.413-1.565, *P* = 0.522). In the subgroup analyses according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT (prophylactic and therapeutic), and presence of portal venous system thrombosis, ascites, and hepatocellular carcinoma, the effects of postoperative use of PPIs on the risk of post-EVT GIB or other post-EVT complications remain not statistically significant.

CONCLUSION

Routine use of PPIs after EVT should not be recommended in patients with liver cirrhosis for the prevention of post-EVT complications during hospitalization.

Key Words: Endoscopic variceal treatment; Gastrointestinal bleeding; Proton pump inhibitors; Complications; Liver cirrhosis; Acute variceal bleeding

Core Tip: The role of proton pump inhibitors (PPIs) in the management of post-endoscopic variceal treatment (EVT) complications remains controversial. We conducted a retrospective study to explore the effects of postoperative use of PPIs on post-EVT gastrointestinal bleeding (GIB) and other post-EVT complications in patients with liver cirrhosis during hospitalization. We found that postoperative use of PPIs was not beneficial for reducing the development of post-EVT GIB and other post-EVT complications during hospitalization. Collectively, routine use of PPIs after EVT during hospitalization may not be recommended, and their indications should be carefully evaluated.

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INTRODUCTION

Acute variceal bleeding (AVB) is a serious complication of liver cirrhosis, indicating the disease progression and development of hepatic decompensation[1,2]. Endoscopic variceal treatment (EVT) is recommended as the major choice for the prevention and treatment of AVB[3,4]. However, the incidence of post-EVT gastrointestinal bleeding (GIB) ranges from 8% to 25%[5,6], which is mainly due to recurrent varices and post-EVT ulcers[7]. In detail, about 4% of patients develop recurrent variceal bleeding after EVT, and 3-25% of patients develop post-EVT ulcer-related GIB[2,8]. Notably, the mortality of GIB secondary to post-EVT ulcer is as high as 52%[2].

Considering the benefits of proton pump inhibitors (PPIs) on the prevention of post-EVT GIB[9,10], the American Society for Gastrointestinal Endoscopy recommends the use of PPIs after endoscopic variceal ligation (EVL) to decrease the rate of ligation-induced ulcer[11] and the Chinese Medical Association also recommends the postoperative use of PPIs to improve the hemostasis success and reduce the rates of ulcer and recent post-EVT GIB[12]. Indeed, the clinicians often use PPIs after EVT in clinical practice[13]. However, the British Society of Gastroenterology states that PPIs are only recommended in the presence of peptic ulcers[14]. Additionally, the Baveno VII consensus also states that patients who used PPIs before EVT should discontinue their use immediately after EVT unless they are strictly indicated[3]. Recent evidence also suggests that the use of PPIs in patients with liver cirrhosis may increase the risk of hepatic encephalopathy and spontaneous bacterial peritonitis[15]. Therefore, whether the routine use of PPIs after EVT is beneficial remains controversial. For this reason, we conducted a retrospective study to evaluate the effects of postoperative use of PPIs on post-EVT GIB and other post-EVT complications in patients with liver cirrhosis during hospitalization.

MATERIALS AND METHODS

Study design

This study was approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command with an approval number [Y (2022) 072] and was performed according to the principles of Declaration of Helsinki. The requirement for patients' informed consent for this study was waived due to its retrospective nature. In this study, we retrospectively reviewed the medical records of 911 patients who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command between January 2016 and June 2020 and treated by an attending physician (XQ)[16-20]. We further selected patients who were diagnosed with liver cirrhosis and underwent EVT during their hospitalization. Exclusion criteria were: 1) patients who developed GIB or were discharged within 24 h after the index EVT; and 2) patients who started the use of PPIs beyond 24 h after the index EVT. Repeated admissions, malignancies, and other comorbidities were not excluded.

Data extraction

By reviewing electronical medical records, demographic data (*i.e.*, age and gender), etiologies of liver cirrhosis, laboratory tests (*i.e.*, white blood cell, hemoglobin, platelet count, total bilirubin, albumin, alanine aminotransferase, serum creatinine, sodium, and international normalized ratio), and other complications of liver cirrhosis [*i.e.*, ascites, jaundice, hepatic encephalopathy, portal venous system thrombosis (PVST)[17], and hepatocellular carcinoma (HCC)] at admission were collected. Model for end-stage liver disease (MELD) score, Child-Pugh score, and Child-Pugh class at admission were calculated[21].

EVT

All EVT procedures were performed by the same experienced endoscopist (XS) at our department[22, 23]. EVL and endoscopic cyanoacrylate glue injection (ECGI) were the first-line choices for the management of esophageal and gastric varices, respectively. Endoscopic injection sclerotherapy (EIS) was performed, if EVL was technically difficult, where active massive bleeding impaired visualization or local scar tissue prevented esophageal varices from being aspirated into the cap to achieve ligation. Indication (*i.e.*, treatment of AVB and primary and secondary prophylaxis of variceal bleeding) and type (*i.e.*, EVL, ECGI and EIS) of EVT and endoscopic findings [*i.e.*, grade of esophageal varices (EVs), red sign of EVs, and active bleeding under endoscopy] were reviewed. The use of PPIs before the index EVT and vasoactive drugs (*i.e.*, octreotide, somatostatin, and terlipressin) after the index EVT were also reviewed. If a patient underwent two or more EVT procedures during the same hospitalization, only the data before the second EVT procedure would be collected.

PPIs after the index EVT

Postoperative PPIs were routinely used in all patients who underwent EVT before January 2018. Since then, this attending physician has systematically reviewed the evidence and questioned the clinical significance of use of PPIs following EVT[10]. Thus, postoperative PPIs would be given on demand if a patient was diagnosed with peptic ulcers, esophageal, gastric, and/or duodenal mucosal erosions, or white nipple signs on endoscopy, developed active variceal bleeding during EVT procedures, or complained of acid-related upper gastrointestinal symptoms (*i.e.*, heartburn and acid regurgitation). Enrollment period, type (*i.e.*, esomeprazole and pantoprazole), route (*i.e.*, intravenous and oral), dosage (*i.e.*, 40 mg once daily, 40 mg twice daily, and 80 mg twice daily), date of starting and discontinuation, and duration of PPIs after the index EVT were reviewed. These data were extracted until post-EVT GIB, the second EVT procedure, or discharge, whichever came first.

Grouping

Patients were divided into PPIs and non-PPIs groups. The PPIs group was defined as patients who had started on PPIs within 24 h after the index EVT for at least one day before post-EVT GIB, the second EVT procedure, or discharge, whichever came first. The non-PPIs group was defined as patients who had not received PPIs after the index EVT until post-EVT GIB, the second EVT procedure, or discharge, whichever came first (Figure 1).

Outcomes

The primary outcome was the development of post-EVT GIB during hospitalization. Post-EVT GIB was defined as the presence of hematemesis, and/or melena, and/or hematochezia, and/or firm clinical or laboratory evidence of acute blood loss from the gastrointestinal tract after the index EVT[24]. Other post-EVT complications included retrosternal pain/discomfort, nausea/vomiting, heartburn/acid regurgitation, fever, diarrhea, and abdominal pain.

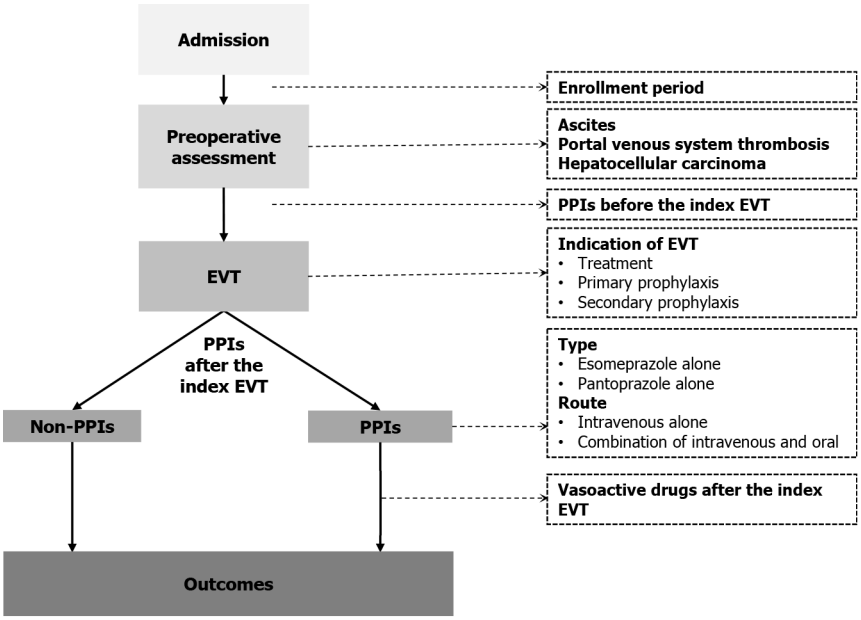

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Figure 1 A schematic chart of study design. EVT: Endoscopic variceal treatment; PPIs: Proton pump inhibitors.

Statistical analyses

All statistical analyses were performed using the IBM SPSS 20.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as median (range) and mean ± standard deviation, and categorical variables were expressed as frequency (percentage). The non-parametric Mann-Whitney U test was used to compare continuous variables between PPIs and non-PPIs groups, and the Chi-square test and Fisher's exact test were used to compare categorical variables between the two groups. Logistic regression analyses were performed to explore the impact of postoperative PPIs on post-EVT GIB and other post-EVT complications during hospitalization. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Subgroup analyses were performed according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT, and presence of PVST, ascites, and HCC (Figure 1). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 148 patients with cirrhosis underwent EVT during their hospitalization. Finally, 143 patients were included (Figure 2). Of them, 83 were in the PPIs group and 60 in the non-PPIs group. The median duration of PPIs administration was 6 (1-13) d. The median hospital stay after EVT was 6 (2-16) d. Patient characteristics are shown in Table 1. Hepatitis B virus infection alone (36.36%) was the most common etiology of liver cirrhosis followed by alcohol abuse alone (23.08%). The median MELD score and Child-Pugh score were 10.24 and 6.00, respectively. Eighty (55.94%), 14 (9.79%), 6 (4.20%), 41 (28.67%), 1 (0.70%), and 1 (0.70%) patient were treated with EVL alone, ECGI alone, EIS alone, EVL combined with ECGI, EIS combined with ECGI, and EVL combined with ECGI and EIS, respectively (Table 2).

Overall analyses

Seven (4.90%) patients developed post-EVT GIB, including three in the PPIs group and four in the non-PPIs group. The median interval between the index EVT and post-EVT GIB was 4 (2-7) d. Only one of them underwent endoscopy and it was found that the source of post-EVT GIB was a post-EVT ulcer. All of them were administered immediately with intravenous vasoactive drugs for the management of post-EVT GIB and two received blood transfusions. Other post-EVT complications were recorded in 67 (46.85%) patients. Logistic regression analyses showed that postoperative use of PPIs was not significantly associated with the risk of post-EVT GIB (OR = 0.525, 95%CI = 0.113-2.438, $P = 0.411$) (Figure 3) or other post-EVT complications (OR = 0.804, 95%CI = 0.413-1.565, $P = 0.522$) (Figure 4).

Table 1 Comparison of baseline characteristics between proton pump inhibitors and non-proton pump inhibitors groups

Variables	Overall		PPIs		Non-PPIs		*P* value
	No.Pts	Median (range), mean ± SD, or frequency (percentage)	No.Pts	Median (range), mean ± SD, or frequency (percentage)	No.Pts	Median (range), mean ± SD, or frequency (percentage)	
Age (yr)	143	56.00 (28.00-88.00)	83	58.00 (30.00-88.00)	60	54.50 (28.00-79.00)	0.089
		55.88 ± 11.77		57.40 ± 11.86		53.78 ± 11.41	
Male	143	104 (72.73%)	83	61 (73.49%)	60	43 (71.67%)	0.809
HBV infection alone	143	52 (36.36%)	83	31 (37.35%)	60	21 (35.00%)	0.773
HCV infection alone	143	11 (7.69%)	83	4 (4.82%)	60	7 (11.67%)	0.202
Alcohol abuse alone	143	33 (23.08%)	83	22 (26.51%)	60	11 (18.33%)	0.252
White blood cell (10^9/L)	141	3.50 (0.80-19.60)	81	3.60 (0.80-19.60)	60	3.45 (1.00-17.40)	0.381
		3.99 ± 2.60		4.15 ± 2.74		3.78 ± 2.40	
Hemoglobin (g/L)	141	89.00 (48.00-155.00)	81	83.00 (48.00-155.00)	60	97.50 (57.00-149.00)	0.081
		93.21 ± 26.69		90.15 ± 27.48		97.35 ± 25.23	
Platelet count (10^9/L)	141	75.00 (15.00-470.00)	81	76.00 (22.00-268.00)	60	71.00 (15.00-470.00)	0.970
		92.58 ± 66.85		87.80 ± 52.28		99.03 ± 82.61	
Total bilirubin (μmol/L)	132	20.40 (5.60-106.10)	74	24.35 (7.00-106.10)	58	16.30 (5.60-96.60)	0.006
		25.67 ± 18.53		28.72 ± 19.92		21.78 ± 15.91	
Albumin (g/L)	133	33.40 (20.50-48.70)	75	31.80 (20.50-45.70)	58	35.30 (21.80-48.70)	0.048
		33.21 ± 5.91		32.41 ± 5.48		34.26 ± 6.32	
Alanine aminotransferase (U/L)	132	20.92 (4.47-1465.50)	74	19.40 (7.57-1465.50)	58	23.62 (4.47-185.02)	0.228
		38.52 ± 127.21		43.85 ± 168.05		31.72 ± 30.61	
Serum creatinine (μmol/L)	135	64.93 (34.51-501.52)	76	64.52 (34.51-117.66)	59	65.21 (36.39-501.52)	0.591
		70.77 ± 42.31		66.97 ± 18.75		75.68 ± 60.31	
Sodium (mmol/L)	134	138.85 (124.00-151.00)	75	138.70 (124.00-151.00)	59	139.00 (133.10-147.70)	0.798
		138.55 ± 3.38		138.49 ± 3.65		138.64 ± 3.04	
International normalized ratio	135	1.29 (0.90-2.55)	75	1.29 (0.90-2.55)	60	1.31 (0.92-2.04)	0.685
		1.36 ± 0.26		1.37 ± 0.27		1.35 ± 0.25	
MELD score	129	10.24 (6.65-30.03)	71	10.51 (6.65-30.03)	58	9.93 (7.14-22.06)	0.214
		11.44 ± 3.78		11.75 ± 4.03		11.05 ± 3.45	
Child-Pugh score	130	6.00 (5.00-12.00)	72	7.00 (5.00-12.00)	58	6.00 (5.00-10.00)	0.388
		6.76 ± 1.59		6.89 ± 1.68		6.60 ± 1.47	
Child-Pugh class							
A		66 (50.77%)		35 (48.61%)		31 (53.45%)	
B	130	57 (43.85%)	72	32 (44.44%)	58	25 (43.10%)	0.709
C		7 (5.38%)		5 (6.94%)		2 (3.45%)	
Ascites	143	75 (52.45%)	83	45 (54.22%)	60	30 (50.00%)	0.618
Jaundice	132	12 (9.09%)	74	9 (12.16%)	58	3 (5.17%)	0.166
Hepatic encephalopathy	143	1 (0.70%)	83	0 (0.00%)	60	1 (1.67%)	0.420

Portal venous system thrombosis	90	39 (43.33%)	55	25 (45.45%)	35	14 (40.00%)	0.611
Hepatocellular carcinoma	143	10 (6.99%)	83	6 (7.23%)	60	4 (6.67%)	1.000

PPIs: Proton pump inhibitors; No. Pts: Numbers of patients; SD: Standard deviation; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MELD: Model for end-stage liver disease.

Table 2 Comparison of endoscopic findings, treatment, and outcomes between proton pump inhibitors and non-proton pump inhibitors groups

Variables	Overall		PPIs		Non-PPIs		*P* value
	No.Pts	Frequency (percentage)	No.Pts	Frequency (percentage)	No.Pts	Frequency (percentage)	
Grade of esophageal varices							
Mild		27 (19.01%)		14 (17.07%)		13 (21.67%)	
Moderate	142	35 (24.65%)	82	21 (25.61%)	60	14 (23.33%)	0.783
Severe		80 (56.34%)		47 (57.32%)		33 (55.00%)	
Red sign of esophageal varices	143	98 (68.53%)	83	57 (68.67%)	60	41 (68.33%)	0.965
Active bleeding	143	5 (3.50%)	83	5 (6.02%)	60	0 (0.00%)	0.074
Indication of EVT							
Treatment		56 (39.16%)		34 (40.96%)		22 (36.67%)	
Primary prophylaxis	143	11 (7.69%)	83	10 (12.05%)	60	1 (1.67%)	0.035
Secondary prophylaxis		76 (53.15%)		39 (46.99%)		37 (61.67%)	
Type of EVT							
EVL		80 (55.94%)		46 (55.42%)		34 (56.67%)	
ECGI		14 (9.79%)		6 (7.23%)		8 (13.33%)	
EIS	143	6 (4.20%)	83	4 (4.82%)	60	2 (3.33%)	0.799
EVL+ECGI		41 (28.67%)		25 (30.12%)		16 (26.67%)	
EIS+ECGI		1 (0.70%)		1 (1.20%)		0 (0.00%)	
EVL+ECGI+EIS		1 (0.70%)		1 (1.20%)		0 (0.00%)	
PPIs before the index EVT	143	66 (46.15%)	83	42 (50.60%)	60	24 (40.00%)	0.209
Vasoactive drugs after the index EVT	143	38 (26.57%)	83	27 (32.53%)	60	11 (18.33%)	0.058
Post-EVT GIB	143	7 (4.90%)	83	3 (3.61%)	60	4 (6.67%)	0.453
Other post-EVT complications	143	67 (46.85%)	83	37 (44.58%)	60	30 (50.00%)	0.521

PPIs: Proton pump inhibitors; No. Pts; Numbers of patients; EVT: Endoscopic variceal treatment; EVL: Endoscopic variceal ligation; ECGI: Endoscopic cyanoacrylate glue injection; EIS: Endoscopic injection sclerotherapy; GIB: Gastrointestinal bleeding.

Subgroup analyses

In all subgroup analyses according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT, and presence of PVST, ascites, and HCC, logistic regression analyses showed that postoperative use of PPIs was not significantly associated with the risk of post-EVT GIB (Figure 3) or other post-EVT complications (Figure 4).

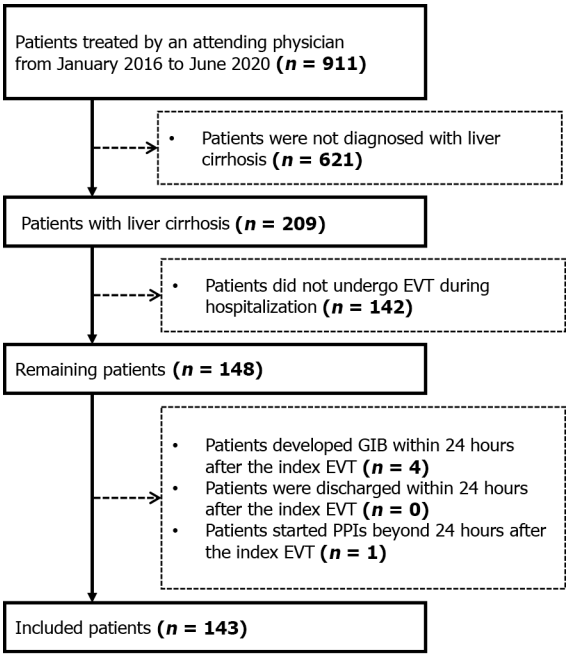

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Figure 2 A flow chart of patients' selection. EVT: Endoscopic variceal treatment; GIB: Gastrointestinal bleeding; PPIs: Proton pump inhibitors.

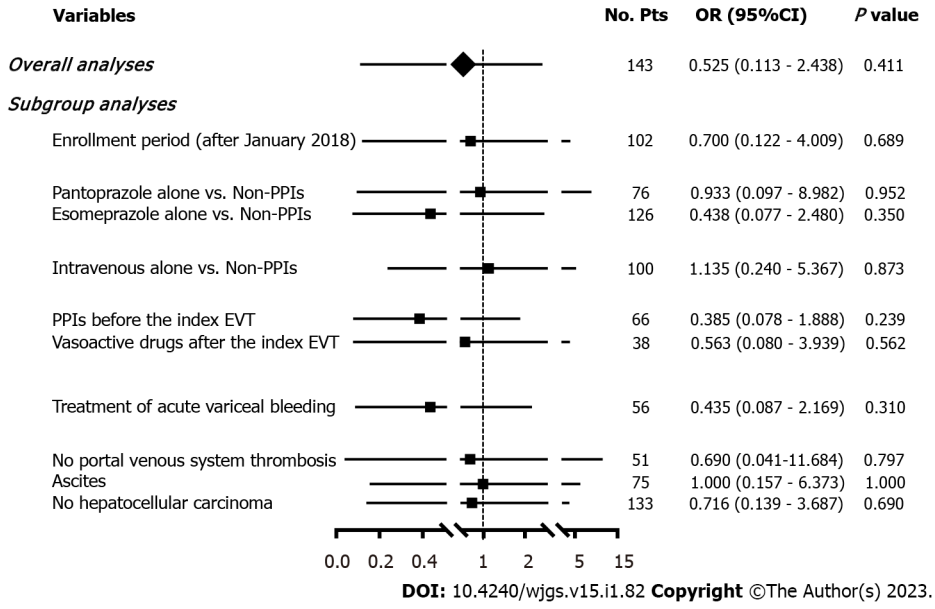

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Figure 3 Forest plots showing the effects of postoperative use of proton pump inhibitors on post-EVT GIB during hospitalization. No. Pts: Numbers of patients; OR: Odds ratio; CI: Confidence interval; PPIs: Proton pump inhibitors; EVT: Endoscopic variceal treatment; GIB: Gastrointestinal bleeding.

DISCUSSION

PPIs are one of the most commonly used drugs in the world[25]. Increasing evidence suggests that the use of PPIs may reduce the abundance and diversity of gut microbiota, leading to the growth of pathogens and the overgrowth of unhealthy species, and that it may be associated with bone fracture, clostridium difficile infection, spontaneous bacterial peritonitis, and hepatic encephalopathy[25,26]. These harms have raised serious concerns about the rational use of PPIs worldwide[27]. Therefore, clinicians should carefully consider the postoperative use of PPIs during hospitalization, and assess the optimal effective dosage and duration of PPIs to avoid their related side effects.

Our study found that postoperative use of PPIs had no significant effect on post-EVT GIB and other post-EVT complications. Our study has several advantages in terms of study design. First, all patients were diagnosed and treated by the same attending physician and all EVT procedures were also performed by the same endoscopist, which avoids heterogeneity in the management of patients. Second,

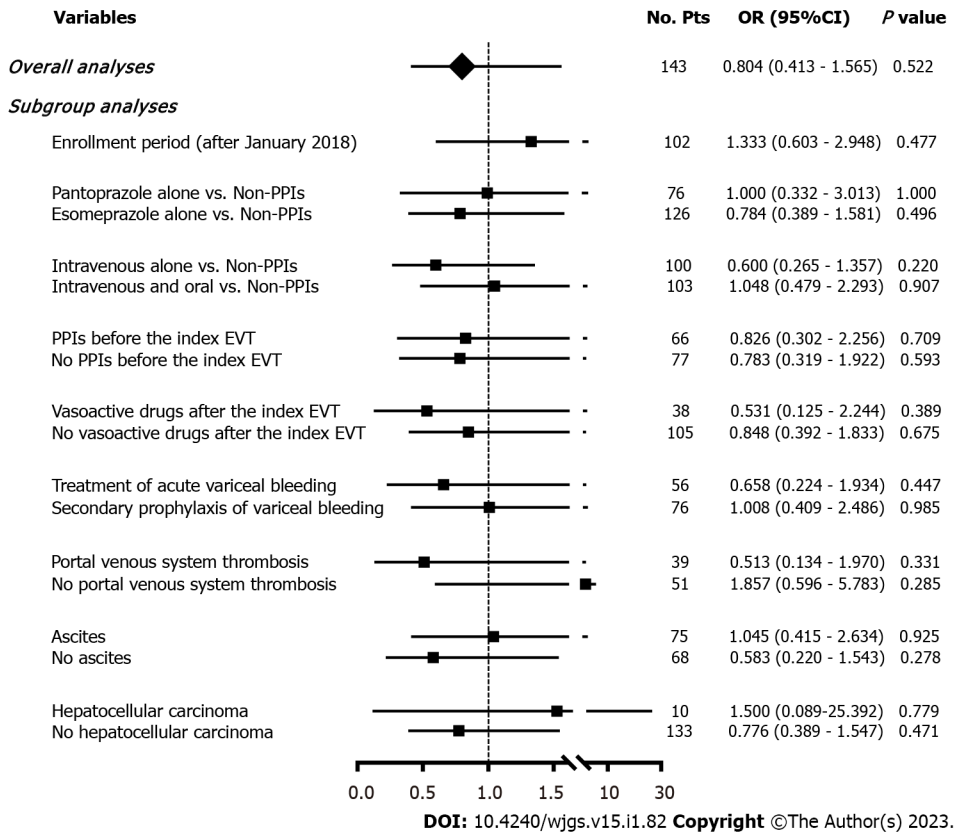

Figure 4 Forest plots showing the effects of postoperative use of proton pump inhibitors on other post-EVT complications during hospitalization. No. Pts: Numbers of patients; OR: Odds ratio; CI: Confidence interval; PPIs: Proton pump inhibitors; EVT: Endoscopic variceal treatment.

patients who underwent prophylactic and therapeutic EVT procedures were both included. Third, subgroup analyses were comprehensively performed according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT (prophylactic and therapeutic EVT), and presence of PVST, ascites, and HCC, which minimizes the impact of confounding factors on statistical results. Fourth, all included patients had been evaluated for at least 24 h since the index EVT, which potentially rules out the effect of technical failure on patients' outcomes.

Post-EVT ulcer, which is one of the main causes of post-EVT GIB, is primarily due to early slippage of rubber bands, sclerosant-induced inflammatory necrosis, and tissue glue-induced caseous necrosis[7,28-31]. It has been traditionally believed that the presence of gastric acid delays ulcer healing[32]. Esophageal motility may be temporarily impaired due to nerve plexus injury after EVT, which delays gastric acid clearance and aggravates the progression of ulcers[33,34]. PPIs are potent acid inhibitors widely used for various acid-related diseases and may promote early healing of post-EVT ulcers by reducing gastric acid secretion, thereby probably decreasing the risk of post-EVT GIB[26,32,35]. In contrast, our study did not demonstrate the benefits of postoperative PPIs in reducing the development of post-EVT GIB. There are some explanations for this unexpected phenomenon. First, post-EVT ulcers are more prone to develop bleeding primarily due to persistent portal hypertension, but not gastric acid [4,31]. Second, the use of PPIs can only reduce the size of ulcers, but not the number of ulcers[36]. Notably, the size of ulcers is not associated with the risk of bleeding[36]. Third, we only observed the impact of short-term use of PPIs on the development of post-EVT GIB during hospitalization. However, post-EVT ulcer healing often requires a duration of about 2 wk[37,38].

Our previous meta-analysis showed a significant benefit of PPIs on post-EVT GIB in patients who underwent prophylactic EVL, but not therapeutic EVT[10]. However, the present study could not confirm the protective effect of postoperative use of PPIs on GIB after prophylactic EVT, because none of the patients who underwent EVT for primary or secondary prophylaxis of variceal bleeding developed post-EVT GIB. Nevertheless, it has been proposed that post-EVL ulcers are usually shallower with only superficial mucosal damage, which may heal more easily with the use of PPIs[37]. Patients who need EVT for the treatment of AVB often have a white nipple, red nipple, or mucosal erosion on endoscopy. Undoubtedly, their conditions are more severe, where the anti-acid effect of PPIs may be insufficient for the improvement of ulcer healing[4].

Except for post-EVT GIB, EVT can also cause other procedure-related complications, which are mild and reversible[3,7]. We did not find any significant effect of PPIs on the development of other post-EVT

complications. This can be explained by the fact that only a fraction of post-EVT complications, such as acid regurgitation and heartburn, are related to gastric acid[39]. By comparison, retrosternal discomfort/pain, nausea, and vomiting are mostly mechanical injuries caused by EVT, and fever may be secondary to bacterial infection[40,41]. Garg *et al*[28] also achieved similar findings, but Lo *et al*[42] showed fewer complications in patients receiving PPIs. Such a discrepancy might be related to the type of complications evaluated, endoscopic techniques, and patients' conditions.

Our study has some limitations. First, the total number of the patients included was small in this study. Second, there were a few cases of post-EVT GIB, which made our statistical analyses underpowered and increased the possibility of type II errors (*i.e.*, false-negative findings). Third, only one patient who developed post-EVT GIB underwent second-look endoscopy, because all of the six patients who developed post-EVT GIB were successfully treated with pharmacotherapy. Fourth, none died of post-EVT GIB or other causes during hospitalization, compromising further analyses regarding the impact of PPIs on death. Fifth, follow-up data were lacking to assess the 6-wk and long-term mortality.

CONCLUSION

Our study suggested that postoperative use of PPIs could not reduce the development of post-EVT GIB and other post-EVT complications during hospitalization. Therefore, PPIs after EVT should not be routinely used during hospitalization, and their indications should be carefully evaluated.

ARTICLE HIGHLIGHTS

Research background

Endoscopic variceal treatment (EVT) is frequently used in cirrhosis with high-risk gastroesophageal varices and acute variceal bleeding. However, it is often associated with a high risk of post-EVT complications, especially postoperative gastrointestinal bleeding (GIB).

Research motivation

The role of proton pump inhibitors (PPIs) after EVT remains controversial.

Research objectives

To evaluate the impact of postoperative use of PPIs on post-EVT GIB and other post-EVT complications in patients with liver cirrhosis during hospitalization.

Research methods

We retrospectively reviewed 911 patients who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command between January 2016 and June 2020 and treated by an attending physician. Logistic regression analyses were performed to explore the impact of postoperative PPIs on post-EVT GIB and other post-EVT complications during hospitalization.

Research results

A total of 143 patients were included. The incidence of post-EVT GIB and other post-EVT complications was 4.90% and 46.85%, respectively. In either overall or subgroup analyses, postoperative use of PPIs did not significantly reduce the risk of post-EVT GIB or other post-EVT complications.

Research conclusions

Postoperative use of PPIs was not beneficial for reducing the development of post-EVT GIB and other post-EVT complications during hospitalization.

Research perspectives

PPIs after EVT should not be routinely used during hospitalization, and their indications should be carefully evaluated. Prospective studies are required to further validate the conclusions of this study.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Associate factors for endoscopic submucosal dissection operation time and postoperative delayed hemorrhage of early gastric cancer

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Abstract

BACKGROUND

Endoscopic submucosal dissection (ESD) is a treatment for early gastric cancer with the advantages of small invasion, fewer complications, and a low local recurrence rate. However, there is a high risk of complications such as bleeding and perforation, and the operation time is also longer. ESD operation time is closely related to bleeding and perforation.

AIM

To investigate the influencing factors associated with ESD operation time and postoperative delayed hemorrhage to provide a reference for early planning, early identification, and prevention of complications.

METHODS

We conducted a retrospective study based on the clinical data of 520 patients with early gastric cancer in the Second Affiliated Hospital of Hainan Medical University from January 2019 to December 2021. The baseline data, clinical features, and endoscopic and pathological characteristics of patients were collected. The multivariate linear regression model was used to investigate the influencing factors of ESD operation time. Logistic regression analysis was carried out to evaluate the influencing factors of postoperative delayed hemorrhage.

RESULTS

The multivariate analysis of ESD operation time showed that the maximum lesion diameter could affect 8.815% of ESD operation time when other influencing factors remained unchanged. The operation time increased by 3.766% or 10.247% if the lesion was mixed or concave. The operation time increased by 4.417% if combined with an ulcer or scar. The operation time increased by 3.692% if combined with perforation. If infiltrated into the submucosa, it increased by 2.536%. Multivariate analysis of delayed hemorrhage after ESD showed that the maximum diameter of the lesion, lesion morphology, and ESD operation time

were independent influencing factors for delayed hemorrhage after ESD. Patients with lesion ≥ 3.0 cm (OR = 3.785, 95%CI: 1.165-4.277), lesion morphology-concave (OR = 10.985, 95%CI: 2.133-35.381), and ESD operation time ≥ 60 min (OR = 2.958, 95%CI: 1.117-3.526) were prone to delayed hemorrhage after ESD.

CONCLUSION

If the maximum diameter of the lesion in patients with early gastric cancer is ≥ 3.0 cm, and the shape of the lesion is concave, or accompanied by an ulcer or scar, combined with perforation, and infiltrates into the submucosa, the ESD operation will take a longer time. When the maximum diameter of the lesion is ≥ 3.0 cm, the shape of the lesion is concave in patients and the operation time of ESD takes longer time, the risk of delayed hemorrhage after ESD is higher.

Key Words: Early gastric cancer; Endoscopic submucosal dissection; Operation time; Delayed hemorrhage

Core Tip: Gastric cancer is a common malignant tumor of the digestive system worldwide. Endoscopic submucosal dissection (ESD) is the first-line treatment for early gastric cancer. However, the long operation time of ESD and its postoperative delayed hemorrhage are the major complications, which can cause more severe cardiovascular complications, such as bradycardia and hypotension. In this retrospective analysis study, the risk factors of long operation time and postoperative delayed hemorrhage were studied. Lesion diameter and shape, ulcer or scar, perforation, and invasion depth all affected the operation time, and lesion diameter, lesion shape, and ESD operation time were independent factors for the occurrence of delayed hemorrhage after ESD.

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INTRODUCTION

Gastric cancer is a malignant tumor originating from the gastric epithelium. Early gastric cancer is generally defined as invasive gastric cancer that invades no more deeply than the submucosa, regardless of lymph node status and metastasis. In 2018, there were 1033701 new gastric cancer cases worldwide, accounting for 5.7% of all types of cancer, making gastric cancer the fifth most common cancer after lung, breast, colorectal, and prostate cancer. In 2018, 782685 patients died of gastric cancer, accounting for 8.2% of all cancer deaths, which is the third major cause of cancer death worldwide[1]. The incidence of gastric cancer is also high in China. According to the latest cancer data statistics in China, 480000 people suffered from gastric cancer in 2020, accounting for 10.5% of all new cancer cases, and 370000 new deaths, accounting for 12.4% of cancer-related deaths, which made gastric cancer the third most deadly cancer among all types of cancers[2]. The good news is the 5-year survival rate of patients with early gastric cancer after active treatment can reach 90%[3]. To date, endoscopic submucosal dissection (ESD) has been used as the first-line treatment for early gastric cancer with the advantages of small invasion, fewer complications, low resection rate, and local recurrence rate[4,5]. However, as a highly sophisticated endoscopic technique, ESD requires advanced endoscopic equipment and skilled operation practices. The risk of complications such as bleeding and perforation is high, and the operation time is also long. Studies have shown that ESD operation time is closely related to bleeding, perforation, postoperative pneumonia, deep vein thrombosis, and carbon dioxide retention, which increases medical costs[6]. The main postoperative complication of ESD was delayed hemorrhage, with an incidence of 4.5%-5.7%. If not treated promptly, it can lead to serious cardiovascular complication[7]. Therefore, this study aims to explore the influencing factors of ESD operation time and postoperative delayed hemorrhage, which would provide a reference for early planning, early identification, and complications prevention of ESD operation.

MATERIALS AND METHODS

Study population

The patients with early gastric cancer who received ESD treatment in the Department Endoscopic Center of the Second Affiliated Hospital of Hainan Medical University from January 2019 to December 2021 were retrospectively analyzed.

Inclusion criteria: (1) Patients with early gastric cancer confirmed by endoscopic biopsy and pathological examination; (2) Patients that found no regional lymph nodes and distant metastasis in endoscopic ultrasonography and other imaging examinations; (3) All patients and their relatives were informed of the risks and benefits of ESD and signed a written informed consent; (4) The patient was informed of the study and agreed to participate; and (5) The patient's information is complete.

Exclusion criteria: (1) Tumor infiltrating into muscular layer or serosa; (2) Patients with severe heart, brain, lung, and other important organ dysfunction; (3) Coagulation dysfunction; (4) Patients with a high risk of anesthesia or intolerance; (5) Suspicious lymph node metastasis; and (6) Two or more lesions appeared.

The baseline data, clinical features, and endoscopic and pathological characteristics of patients were collected, including gender, age, underlying diseases, medication history, lesion location, lesion shape, maximum lesion diameter, ulcer and scar, perforation, pathological diagnosis, depth of invasion, delayed hemorrhage and ESD operation time (min).

ESD operation process and postoperative treatment

GIFQ260J gastroscope with an additional water supply function was used (Olympus, Japan). The front end of the gastroscope is provided with a soft transparent cap (Olympus, Japan). High-frequency electrical uses erbotomicc200 or vio200d (Erbe, Germany). Under general anesthesia, the submucosal injection during ESD operation consisted of glycerol, fructose solution, an appropriate amount of methylene blue, and epinephrine at a ratio of 1:10000. Sodium hyaluronate solution was diluted with normal saline (1:5) when necessary. The lesion was located under endoscopy, and the boundary between the lesion and the normal mucosa was determined by NBI amplification and 2.5% Lugol solution staining. Thermocoagulation markers were made around the lesion every 0.5 cm from 0.3 to 0.5 cm from the lesion border. The mucosa and submucosa were separated by submucosal injection along the lesion boundary. An incision was cut at about 0.5 cm outside the marker, and then the lesion was cut along the mucosa of the lesion edge with a dual knife until the submucosa was reached, and the lesion was gradually stripped along the submucosa. During the stripping, the hemostatic forceps were used intermittently until the tumor was completely stripped. Finally, thermal hemostatic forceps were used to stop the wound, and titanium clips were used to seal the wound for patients with deep dissection or cracks in the muscularis propria. The vital signs of patients were closely monitored after the operation. In this study, all ESD procedures were performed by a professional endoscopic physician with more than 15 years of technical experience using the same equipment.

The postoperative treatment and follow-up measures of ESD included postoperative placement of a gastric tube. According to the needs of the patient, the patient was fasted for 3-5D and received hemostasis, acid suppression, anti-infection, and intravenous nutritional support. Gastric tube drainage and patients with abdominal pain, abdominal distension, and other signs were closely observed. Patients continued to take gastric mucosal protective agents and proton pump acid inhibitors for 8 wk after discharge. The endoscopic review was performed once every 3, 6, and 12 mo after the operation, and then once a year. Postoperative chest and abdomen computed tomography examination was performed once a year.

ESD operation time is defined as the time (min) from the circumferential marking of the lesion to the complete resection of the lesion. Delayed hemorrhage was considered by the following situations within 24 h to 30 d after ESD: (1) Vomiting, dizziness, melena, and other symptoms; (2) Blood pressure drop > 20 mmHg or heart rate increase by 20 times/min; (3) Endoscopic examination confirmed surgical wound bleeding; and (4) Hemoglobin level decreased ≥ 2 g/dL after endoscopic treatment. At the time of discharge, researchers instructed patients on how to identify delayed bleeding, and collected patients' delayed bleeding by phone or face-to-face after discharge.

Ethical principles

This study is a retrospective study. All patient data obtained, recorded, and managed will be used for this study only, and all patient information will be kept strictly confidential and will not cause any harm to the patient. In addition, the research scheme was approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical University.

Statistical analysis

SPSS26.0 statistical software was used for statistical analysis. The numerical variables that meet the normal distribution were described by mean ± SD, and the classification variables were described by frequency (percentage). The influencing factors of ESD operation time were analyzed by univariate

analysis and multivariate analysis. In single-factor analysis, Pearson correlation analysis was used for age, independent sample *t*-test was used for two classification factors, variance analysis was used for multi-classification factors, and LSD test was used for pairwise comparison. The multivariate linear regression model was used for the multivariate analysis of ESD operation time. Also, a single-factor analysis of delayed hemorrhage after the operation was performed by χ^2 test, and multivariate logistic regression analysis was used to analyze the influencing factors of delayed hemorrhage after ESD. Test level $\alpha = 0.05$.

RESULTS

Patient characteristics

From January 2019 to December 2021, there were 551 patients with early gastric cancer received ESD treatment in total in our endoscopic center. As shown in the figure, endoscopy confirmed early gastric cancer (Figure 1A and B). Among them, 24 patients had incomplete data, and 7 patients did not meet the criteria for admission and discharge. Therefore, 520 patients with early gastric cancer were collected for this retrospective study. There were 367 males and 153 females, with a ratio of 2.40:1. The age of patients was between 31 and 84 years old and the average age was 57.81 ± 10.56 years old. The median maximum diameter of the lesion was 3.0 cm, ranging from 0.35 cm to 10.55 cm. The average operation time was 66.78 ± 40.89 min (10-160 min). In total, 508 (97.69%) lesions were completely resected, and 499 (95.96%) lesions met the standard of curative resection. There were 189 cases of upper gastric lesions, 112 cases of middle gastric lesions, and 219 cases of lower gastric lesions. Delayed hemorrhage occurred in 43 patients after ESD (8.27%). Hemorrhage patients underwent emergency endoscopic hemostasis and hemostasis was successful. 11 patients needed a blood transfusion.

Single-factor analysis of ESD operation time

The results of the single-factor analysis were shown in Table 1. Patients with maximum lesion diameter ≥ 3.00 cm had longer ESD operation time than patients with lesion diameter < 3.00 cm. The operation time of ESD in patients with different lesions was different, mixed type > concave type > flat type > uplift type. The operation time of patients with ulcers or scars was longer than those of patients without ulcers. Patients with perforation were longer than those without perforation. Patients with perforations had a longer duration of disease than those without. Lesions infiltrated into the submucosa more frequently than into the mucosa alone. And the differences were all statistically significant ($P < 0.05$).

Multivariate analysis of ESD operation time

The ESD operation time (min) was taken as the dependent variable Y, and the variables with statistical significance in single factor analysis were taken as independent variables Xi. The multiple linear regression model was fitted by a stepwise method. The goodness of fit of the multiple linear regression model reached a large effect ($r = 0.692$). The model finally adjusts R^2 was 0.563. The variance analysis results of the model showed that the F value was 54.866, and the P value was < 0.001. The regression equation was as follows: In = 21.674 + 8.815 × 1 + 3.766 × 2 + 10.247 × 3 + 4.417 × 4 + 3.692 × 5 + 2.536 × 6. When other factors remain unchanged, the maximum diameter of the lesion can affect the ESD operation time by 8.815%. If the lesion was concave or mixed, the operation time increased by 3.766% or 10.247%. If combined with an ulcer or scar, ESD operation time increased by 4.417%. The operation time increased by 3.692% if combined with perforation. If infiltrated into the submucosa, it increased by 2.536% (Table 2).

Single-factor analysis of delayed hemorrhage after ESD

The subjects were divided into a bleeding group and a non-bleeding group according to whether postoperative delayed hemorrhage occurred. The results of the single-factor analysis were shown in Table 3. Patients with hypertension, a history of taking anticoagulant or antiplatelet drugs, maximum lesion diameter, lesion morphology, and ESD operation time were associated with postoperative delayed hemorrhage ($P < 0.05$). Gender, age, other underlying diseases except for hypertension, location of lesion, ulcer or scar, perforation, and depth of infiltration were not associated with delayed hemorrhage after the operation ($P > 0.05$).

Multivariate analysis of delayed hemorrhage after ESD

Taking the occurrence or not of delayed hemorrhage after ESD as the dependent variable, and the factors with statistical significance in single factor analysis as independent variables, the multivariate logistic regression model was fitted. As shown in Table 4. The maximum diameter of lesions, lesion morphology, and ESD operation time were independent factors for delayed hemorrhage after ESD. Patients with lesions ≥ 3.0 cm (OR = 3.785, 95%CI: 1.165-4.277), lesion morphology-concave type (OR = 10.985, 95%CI: 2.133-35.381), and ESD operation time ≥ 60 min (OR = 2.958, 95%CI: 1.117-3.526) were prone to delayed hemorrhage after ESD.

Table 1 Single-factor analysis of endoscopic submucosal dissection operation time

Factors	*n*	Operation time (min) (mean ± SD)	*r*/*t*/*F*	*P* value
Age (yr)	520	66.78 ± 40.89	0. 191	0.812
Sex			0.311	0.764
Male	367	64.19 ± 41.21		
Female	153	73.38 ± 35.82		
Underlying diseases			0.921	0.146
None	379	63.11 ± 27.17		
Hypertension	126	70.91 ± 32.19		
Diabetes	12	67.24 ± 41.65		
Cirrhosis	3	78.55 ± 30.52		
History of taking anticoagulant or antiplatelet drugs			1.260	0.262
Yes	31	59.51 ± 48.44		
No	489	66.12 ± 20.38		
Lesion location			1.333	0.198
Upper gastric body	112	75.76 ± 31.76		
Middle gastric body	70	63.36 ± 38.91		
Lower gastric body	338	65.54 ± 39.18		
Maximum diameter of lesion			8.691	< 0.001
< 3.00 cm	351	52.22 ± 29.81		
≥ 3.00 cm	169	90.38 ± 40.21		
Lesion form			11.123	< 0.001
Uplift type	134	48.54 ± 28.11		
Flat type	138	53.66 ± 31.81		
Concave type	91	71.17 ± 33.71		
Mixed type	157	109.33 ± 40.28		
Combined ulcer or scar			7.288	0.001
Yes	64	93.17 ± 37.34		
No	456	62.36 ± 31.97		
Combined perforation			9.327	< 0.001
Yes	21	121.33 ± 41.19		
No	499	63.17 ± 36.85		
Infiltrative depth			5.442	0.017
Mucosa	397	55.44 ± 36.18		
Submucosa	123	87.23 ± 39.67		

DISCUSSION

In the past, surgical resection is the standard treatment for early gastric cancer. However, conventional surgery has the disadvantages of large invasion, more postoperative complications, and longer recovery time[8]. Compared to surgical resection, ESD has the advantage of small invasion, more tolerable for patients. And it also can be used as multiple surgical treatments for the same patient or multiple parts of treatment at the same time. Moreover, it has been recognized by experts all over the world and has been used as the first-line treatment for early gastric cancer[9,10]. The amount of time for an ESD is one of the best indicators to measure the difficulty of surgical operation. And IT is very beneficial for the operation plan arrangement and complications prevention if the difficulty and operation time could be predicted in advance. In previous studies, the multivariate analysis suggested that tumor location and size were

Table 2 Indigenous test results of multivariate linear regression independent variables

Factors	Unstandardized β value	Sx value	Standardized β value	*t* value	*P* value
Intercept	21.674	0.433	-	36.188	< 0.001
Maximum diameter of lesion	8.815	0.684	0.732	3.812	< 0.001
Lesion form - flat	1.277	1.475	0.032	0.333	0.493
Lesion form - concave type	3.766	0.872	0.383	4.456	< 0.001
Lesion form - mixed	10.247	0.929	0.633	9.580	< 0.001
Combined ulcer or scar	4.417	0.305	0.180	3.154	0.007
Combined perforation	3.692	2.303	0.153	2.340	0.020
Infiltrative depth - submucosa	2.536	0.569	0.077	2.652	0.008

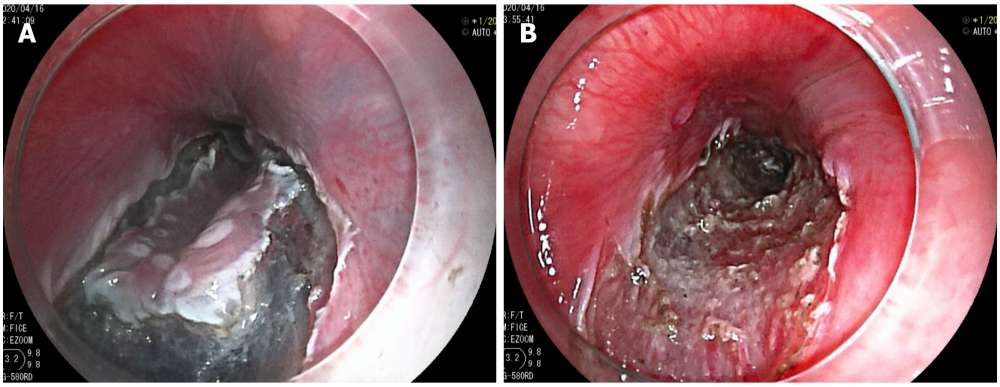

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Figure 1 Process picture of endoscopic submucosal dissection for early gastric cancer. A: Under gastroscope, gastric mucosal lesions in the anterior wall of the gastric body can be seen. Mucosal resection was performed along the periphery of the lesion; B: Wound map after mucosa stripping.

important predictors of operation time[11,12]. The operation difficulty of different positions of the gastric cavity varies greatly, which will affect the operation time of ESD[13]. In this study, the same equipment and the ESD operation method were used by the same surgeon, which means the influence of different equipment on ESD operation time was excluded. Single-factor and multi-factor analyses were conducted after excluding the above-mixed factors. We found that the maximum diameter of the lesion, lesion morphology, ulcer or scar, perforation, and depth of invasion were independent factors affecting the ESD operation time. Previous studies found that intraoperative perforation was an independent predictor of prolonged ESD operation time[14,15]. Our research also has similar conclusions. In ESD, small perforations can be treated under endoscopy, and the operation time will be prolonged due to the need for metal clips to seal the wound[16]. Longer operation time can increase the risks of complications[17]. Therefore, shortening ESD operation time can reduce intraoperative and postoperative complications of ESD[18]. Thus, the prediction of operative time is crucial for both patients and surgeons. First of all, if we can predict if it will be a longer operation time, we can arrange for senior experts to complete difficult and long-term surgery, and shorten the operation time. Secondly, according to the length of the operation time, anesthesiologists can also use different anesthesia methods. Finally, the prediction of operation time can help operators to take corresponding measures to prevent complications in time, such as venous thrombosis, intraoperative aspiration, or postoperative pneumonia. However, the ESD operation technique is difficult, and the incidence of complications such as bleeding and perforation is high[19]. Usually, intraoperative bleeding and perforation can be treated immediately. But delayed bleeding can lead to severe consequences such as hemorrhagic shock if it is found and treated not timely[20]. Generally, artificial ulcers formed by ESD turn into fibrosis and thicken the gastric wall around 2 wk after surgery, and the healing takes about 8 wk[21]. Some studies have shown that about 1/4 of the artificial ulcers appear as visible blood vessels on the 3rd day after ESD, and these broken blood vessels may be one of the main reasons for postoperative delayed bleeding [22].

Among the 520 patients in this study, there were 43 (8.27%) patients with postoperative delayed bleeding, which was aligned with other literature. Takeuchi *et al*[23] retrospectively analyzed the data of 833 patients with early gastric cancer and precancerous lesions treated with ESD. and found that the longer duration of ESD in gastric cancer patients was an important risk factor for postoperative

Table 3 Single-factor analysis of the bleeding group and non-bleeding group

Factors	Bleeding group (n = 43)	Non-bleeding (n = 477)	χ^2 value	P value
Age (yr)			0.120	0.729
< 60	23	242		
≥ 60	20	235		
Sex			0.015	0.903
Male	30	337		
Female	13	140		
Underlying diseases				
Hypertension	16	110	4.301	0.038
Diabetes	2	10	1.142	0.285
Cirrhosis	0	3	-	-
History of taking anticoagulant or antiplatelet drugs			59.148	< 0.001
Yes	14	17		
No	29	460		
Lesion location			0.489	0.783
Upper gastric body	10	102		
Middle gastric body	7	63		
Lower gastric body	26	312		
Maximum diameter of lesion			29.677	< 0.001
< 3.00 cm	13	338		
≥ 3.00 cm	30	139		
Lesion form			11.098	0.011
Uplift type	7	127		
Flat type	12	126		
Concave type	15	76		
Mixed type	9	148		
Combined ulcer or scar			0.020	0.887
Yes	5	59		
No	38	418		
Combined perforation			1.044	0.307
Yes	3	18		
No	40	459		
Infiltrative depth			3.274	0.070
Mucosa	28	369		
Submucosa	15	108		
ESD operation time			6.979	0.008
< 60 min	16	277		
≥ 60 min	27	200		

ESD: Endoscopic submucosal dissection.

bleeding. Previous studies have shown that the lesion size after ESD is the only risk factor for delayed bleeding[24,25]. Resection of large lesions can cause more damage to gastric wall blood vessels, and the risk of postoperative bleeding is higher. The results of this study further confirmed the conclusion that a

Table 4 Logistic regression analysis of delayed hemorrhage after endoscopic submucosal dissection

Factors	β	S_x	Wald value	OR (95%CI)	*P* value
Hypertension					
No				1	
Yes	0.776	0.522	2.175	2.137 (0.912-2.643)	0.136
Taking anticoagulants					
No					
Yes	1.841	1.062	2.851	4.377 (0.657-37.912)	0.078
Maximum diameter of lesion					
< 3.00 cm				1	
≥ 3.00 cm	0.941	0.347	7.399	3.785 (1.165-4.277)	0.011
Lesion form					
Uplift type				1	
Flat type	0.701	1.031	0.452	2.011 (0.251-15.664)	0.072
Concave type	2.378	1.679	4.917	10.585 (2.133-35.381)	0.007
Mixed type	1.327	1.720	0.873	2.816 (0.463-19.832)	0.254
ESD operation time					
< 60 min				1	
≥ 60 min	1.446	1.271	3.541	2.958 (1.117-3.526)	0.011

ESD: Endoscopic submucosal dissection.

lesion ≥ 3 cm was more likely to postoperative bleeding. This suggests that endoscopic surgeons need to control the resection area as much as possible during the operation to avoid more gastric mucosal damage. We used magnifying and narrow-band imaging electronic chromoendoscopy to accurately determine the lesion boundary before surgery, and then accurately remove the lesion, which well controlled the operational area of surgical resection.

Previous studies have shown that flat lesions and concave lesions are associated with delayed bleeding after ESD. The results of this study suggested that concave lesions were more likely to have postoperative delayed bleeding (P = 0.007). This result can be explained by the following reasons. Firstly, compared with the uplift lesions, the concave lesions were closer to the muscular layer, and inappropriate biopsy can cause submucosa fibrosis easily, which leads to the increased probability of intraoperative bleeding. Furthermore, the submucosal vessels of flat lesions were richer than those of uplift lesions, thus, the risk of postoperative bleeding was higher. Long operation time is usually associated with frequent dissection and unskilled operation. Unskilled operation and repeated dissection often lead to vascular injury in the lower gastric mucosa and muscularis propria, which is easy to cause early postoperative delayed bleeding. Large lesions and deep infiltration, combined with perforation, can increase the difficulty of mucosal dissection and operation time and therefore easily damage blood vessels. Taking anticoagulant or antiplatelet drugs can inhabit ulcer-induced proliferation of gastric epithelial cells, thereby inhibiting angiogenesis during gastric ulcer healing, resulting in delayed bleeding more likely after ESD. It has been shown to be an independent risk factor for delayed bleeding after early and late ESD[26,27]. Studies have found that antithrombotic drugs are independent risk factors for bleeding after ES[25]. However, there was no significant difference in the distribution of aspirin administration history between the bleeding group and the non-bleeding group in this study. This may be the following reasons: Patients were required to discontinue anticoagulant drugs for one week before ESD or replace other drugs under the guidance of cardiovascular physicians. Patients with severe cardiovascular diseases were not treated in the department, so there was a selection bias in this study. It may also be related to the small sample size. This study was a single-center retrospective analysis with limited sample size and possible bias that was difficult to eliminate.

CONCLUSION

In summary, patients with early gastric cancer with a maximum lesion diameter ≥ 3.0 cm, concave

morphology, associated ulceration or scarring, combined perforation, and infiltration into the submucosa had a longer ESD operation time. Most importantly, the risk of delayed bleeding after ESD is higher when the maximum diameter of the lesion is ≥ 3.0 cm, the lesion morphology is concave, and the ESD operation time is longer. Therefore, we suggest that such patients should be treated with caution. Before the operation, the risk should be fully assessed. During the operation, the bleeding should be strictly controlled and the wound should be properly handled. The operation should also be carried out by experienced physicians. Finally, close observation also should be performed after the operation.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) has become a new development trend in the treatment of early gastric cancer due to its special minimally invasive advantages. Although it is minimally invasive surgery, it also has some risks such as bleeding and perforation.

Research motivation

The time of ESD operation is closely related to bleeding and perforation.

Research objectives

This study aims to investigate the operation time of endoscopic subspecific section and the influencing factors of delayed bleeding after operation.

Research methods

The baseline data, clinical features, and endoscopic and pathological characteristics of patients were collected. The multivariate linear regression model was used to investigate the influencing factors of ESD operation time. Logistic regression analysis was carried out to evaluate the influencing factors of postoperative delayed hemorrhage.

Research results

The maximum diameter of the lesion, lesion morphology, and ESD operation time were independent influencing factors for delayed hemorrhage after ESD. Patients with lesion ≥ 3.0 cm (OR = 3.785, 95%CI: 1.165-4.277), lesion morphology-concave (OR = 10.985, 95%CI: 2.133-35.381), and ESD operation time ≥ 60 min (OR = 2.958, 95%CI: 1.117-3.526) were prone to delayed hemorrhage after ESD.

Research conclusions

The risk of delayed bleeding after ESD is higher when the maximum diameter of the lesion is ≥ 3.0 cm, the lesion morphology is concave, and the ESD operation time is longer.

Research perspectives

Further research should be made on other factors related to delayed bleeding after ESD operation, such as factors during operation and individual related factors. Strict control of surgical indications and adherence to individualized treatment can help reduce the occurrence of complications.

FOOTNOTES

Author contributions: Cai RS designed this study, analyzed the data and drafted the manuscript; Yang WZ and Cui GR collected the data and reviewed the manuscript critically; all authors have read and approved the final manuscript version.

Institutional review board statement: The study was reviewed and approved by Ethics Committee of the Second Affiliated Hospital of Hainan Medical University.

Informed consent statement: The data used in this study were not involved in the patients' privacy information, so the informed consent was waived by the Ethics Committee of Second Affiliated Hospital of Hainan Medical University. All patient data obtained, recorded, and managed only used for this study, and all patient information are strictly confidential, without any harm to the patient.

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Short-term efficacy assessment of transarterial chemoembolization combined with radioactive iodine therapy in primary hepatocellular carcinoma

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Abstract

BACKGROUND

Transarterial chemoembolization (TACE) is an effective treatment for primary hepatocellular carcinoma (PHC). Radioactive iodine therapy has been used in the treatment of advanced PHC, especially in patients with portal vein tumor thrombosis. However, data on the therapeutic effect of TACE combined with radioactive iodine therapy in PHC are scarce.

AIM

To investigate the clinical efficacy of TACE combined with radioactive iodine implantation therapy in advanced PHC *via* perfusion computed tomography (CT).

METHODS

For this study, 98 advanced PHC patients were recruited and divided randomly into the study and control groups. Patients in the study group were treated with TACE combined radioactive iodine implantation therapy. Patients in the control group were treated with only TACE. The tumor lesion length, clinical effect, serum alpha-fetoprotein (AFP) and CT perfusion parameters were compared

before and after therapy, and statistical analysis was performed.

RESULTS

There was no significant difference in tumor length and serum AFP between the study and control groups ($P > 0.05$) before treatment. However, the tumor length and serum AFP in the study group were lower than those in the control group 1 mo and 3 mo after therapy. After 3 mo of treatment, the complete and partial remission rate of the study group was 93.88%, which was significantly higher than the control group (77.55%) ($P < 0.05$). Before treatment, there were no significant differences between the two groups on the perfusion CT variables, including the lesion blood volume, permeability surface, blood flow, hepatic artery flow and mean transit time ($P > 0.05$). After 3 mo of treatment, all perfusion CT variables were lower in the study group compared to the control group ($P < 0.05$). The survival time of patients in the study group was 22 mo compared to 18 mo in the control group, which was significantly different [log rank (Mantel-Cox) = 4.318, $P = 0.038$].

CONCLUSION

TACE combined with radioactive iodine implantation in the treatment of advanced PHC can inhibit the formation of blood vessels in tumor tissue and reduce the perfusion level of tumor lesions, thereby improving the clinical efficacy and prolonging the survival time of patients.

Key Words: Transarterial chemoembolization; Radioactive iodine; Primary hepatocellular carcinoma; Perfusion; Computed tomography

Core Tip: This randomized controlled trial was designed to investigate the short-term clinical efficacy of transarterial chemoembolization (TACE) combined with radioactive iodine implantation in the treatment of patients with primary hepatocellular carcinoma (PHC). The results demonstrated that this treatment could inhibit the formation of blood vessels in tumor tissue and reduce the perfusion level of tumor lesions better than TACE alone. Therefore, TACE combined with radioactive ion implantation could improve the clinical efficacy and prolong the survival time of patients with PHC.

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INTRODUCTION

Primary hepatocellular carcinoma (PHC) is a malignant tumor with a high incidence in the Chinese population. It can develop in hepatocytes and intrahepatic bile duct cells and cause clinical symptoms[1-3]. Surgical resection is the primary treatment for early-stage hepatocellular carcinoma. However, due to an insidious onset and atypical early symptoms, more than 80% of hepatocellular carcinoma patients are diagnosed with metastasis and are ineligible for surgical treatment[1,4-6].

Transarterial chemoembolization (TACE) is the main treatment for patients with inoperable hepatocellular carcinoma. It can release chemotherapeutic drugs rapidly and maintain a high blood concentration in the organ to inhibit rapid local tumor growth. However, its long-term efficacy is inadequate[5-8]. Radioactive iodine (^{125}I) implantation is a new means of radiotherapy with a high radiation dose and precise localization. It is also a potential treatment option for patients with PHC[8-11]. As such, this study investigated the short-term clinical efficacy of TACE combined with ^{125}I implantation in the treatment of patients with PHC.

MATERIALS AND METHODS

Patient data

From January 2016 to June 2018, 98 patients with PHC, who were scheduled for treatment with

interventional embolization chemotherapy, were selected as study subjects. They were randomly divided into the study group (n = 49) and the control group (n = 49). The inclusion criteria included: (1) Diagnosis of PHC according to the criteria in the Guidelines for Diagnosis and Treatment of Primary Hepatocellular Carcinoma[10,12-15]; (2) PHC confirmed by computed tomography (CT), magnetic resonance imaging and liver puncture biopsy; (3) Patients aged 19-79 years; (3) PHC patients with preoperative liver function grade A or B according to the Child-Pugh classification; (4) Stage C and D lesions according to the Barcelona Clinic Liver Cancer (BCLC) staging system[10,12-15]; (5) Preoperative assessment of survival time > 3 mo; and (6) PHC patients with survival status score 0-2 based on the Eastern Cooperative Oncology Group Performance Status[13]. The exclusion criteria included: (1) Metastatic hepatocellular carcinoma; (2) Biliary obstruction due to tumor infiltration of the bile duct; (3) Hepatic artery-portal vein fistula formation; (4) Mental illness and intellectual disability; (5) Severe renal dysfunction; and (6) Other contraindications to treatment. Study protocols were reviewed by ethics experts and implemented with presurgical informed consent from patients and families.

Methods

Treatment method: The control group was treated with TACE, which included the following chemotherapy drugs: 0.75-1.25 g of 5-fluorouracil; 80-120 mg of cisplatin; 20 mg of oxaliplatin; 80-140 mg of epirubicin; and super-liquidated iodine oil as an embolic agent. The doses of chemotherapy drugs and iodine oil were adjusted according to the tumor size and blood supply.

The study group was treated with TACE combined with ^{125}I implantation. After 1 wk of TACE, a CT scan was performed to confirm the location, structure and specific size of the tumor and its surrounding tissues, and CT navigation and localization were performed. ^{125}I particles were placed in the patients after CT determined that the needle tip reached the target area, and the distribution was recorded. The puncture needle was withdrawn after successful placement was confirmed by CT scan, and the site was sterilized and bandaged.

Evaluation indices: After being admitted and treated, 3 mL of venous blood was drawn to measure serum alpha-fetoprotein (AFP) by enzyme-linked immunoassay using an enzyme-labeled instrument (BD Biosciences, Franklin Lakes, NJ, United States). The CT perfusion parameters measured were blood volume (BV), permeability surface (PS), blood flow (BF), hepatic artery flow (HAF), and mean transit time (MTT).

Lesions were classified as complete remission (CR), partial remission (PR), stable disease and progressive disease according to the changes in the lesions before and after treatment. CR was defined as solid tumors, other than nodal disease, where the target lesion completely disappeared or all target nodes had shrunk to normal size for 4 wk or more. PR was defined as the sum of long diameters selected for target lesions and short diameters selected for target nodes reduced by ≥ 30% when compared to baseline for 4 wk or more. Progressive disease was defined by the sum of the target lesion diameters exceeding the reference value (smallest sum of the measured target lesion diameters) by 20% or more and the absolute value increased by ≥ 5 mm or ≥ 1 new lesions having appeared and not completely/partially in remission before the lesions grew in size or increased in number. Stable disease was defined when the volume and number of lesions were between PR and progressive disease.

Statistical processing

SPSS 21.0 software (IBM Corp., Armonk, NY, United States) was used for statistical comparative analysis of the data. The measurement data, such as tumor length and AFP level, were expressed by mean ± SD, and the t test was adopted for comparison between groups. χ^2 test was adopted for comparative analysis between groups (clinical efficacy and other count data). The Kaplan-Meier method was used to model the survival analysis. $P < 0.05$ was considered a statistically significant difference.

RESULTS

Comparison of baseline characteristics between the two groups

In the study group, the patients ranged from 43-years-old to 76-years-old (56.3 ± 7.2 years) and included 28 males and 21 females. Thirty patients were BCLC stage C and 19 patients were BCLC stage D. The maximum diameter of the tumor lesion was 6.31 ± 2.00 cm. There were 32 cases of Child-Pugh grade A and 17 cases of Child-Pugh grade B PHC. In the control group, the patients ranged from 40-years-old to 75-years-old (55.5 ± 6.8 years) and included 31 males and 18 females. There were 34 cases of BCLC stage C and 15 cases of BCLC stage D. The maximum diameter of tumor lesion was 6.14 ± 1.89 cm. There were 30 cases of Child-Pugh grade A and 19 cases of Child-Pugh grade B PHC. There were no statistically significant differences between these baseline characteristics of the two groups ($P > 0.05$).

Comparison of changes of tumor lengths between the two groups

Before treatment, there was no statistically significant difference in tumor lengths between the study group and the control group ($P > 0.05$). The tumor lengths of the study group were significantly lower

than those of the control group after 1 mo and 3 mo of treatment ($P < 0.05$) (Table 1 and Figure 1A).

Comparison of changes in serum AFP levels in the two groups of patients

Before treatment, the difference in serum AFP between the study group and the control group were not statistically significant ($P > 0.05$). After 1 mo and 3 mo of treatment, the serum AFP of the study group was lower than that of the control group ($P < 0.05$) (Table 2 and Figure 1B).

Comparison of treatment efficacy in the two groups of patients

After 3 mo of treatment, the CR + PR rate in the study group was 93.88%, which was higher than in the control group (77.55%, $P < 0.05$) (Table 3).

Comparison of CT perfusion parameters of tumor lesions in the two groups

Before treatment, there was no statistically significant difference between the BV, PS, BF, HAF and MTT measurements of the lesions in the study group and the control group ($P > 0.05$). After 3 mo, the BV, PS, BF, HAF and MTT measurements in the study group were lower than those in the control group ($P < 0.05$) (Table 4).

Comparative analysis of survival between the two groups of patients

The patients in both groups were followed up and observed. There was no statistically significant difference between the 3-year survival rate of patients in the study group and the control group ($P > 0.05$). However, the survival time of patients in the study group was 22 mo, which was significantly longer than 18 mo in the control group [log rank (Mantel-Cox) = 4.318, $P = 0.038$] (Table 5 and Figure 2).

DISCUSSION

Epidemiological studies suggest that the incidence rate of liver cancer in China has reached 29/100000, with a mortality rate of 26.04/100000[3,10,12,16]. PHC is caused by various factors including hepatitis B virus infection, aflatoxin, toxic substances, alcohol, nitrite, environmental pollution, *etc*[7,11,15,17]. Surgery is the most effective treatment for PHC. However, due to insidious early symptoms, the time for surgical treatment is often missed[10,17-19].

TACE is the first choice of treatment for inoperable liver cancer surgery[7,20,21]. It directly delivers embolic agents, iodinated oil and chemotherapeutic drugs, which can cause tumor ischemia and hypoxia, and are injected into the hepatic artery through a catheter. This catheter also blocks the blood supply, which inhibits tumor growth and metastasis[1,7,11,18,21]. Unfortunately, as the clinical utilization of TACE increased, several disadvantages were found, including need for multiple treatments, incomplete embolizations, and increased chance of recurrence and metastasis due to vascular endothelial growth factor release. A single TACE treatment typically has a dissatisfactory long-term treatment effect.

^{125}I implantation is a new minimally invasive interventional technique that is effective in treating lung cancer, liver cancer, and kidney cancer[8-11]. Radioactive particles, like ^{125}I, are encased in a very small silver rod or titanium alloy and form a very small particle that contains a very strong radioactive isotope [8,9,11]. ^{125}I particles are a type of brachytherapy. Due to the shorter range (1 cm action radius), lower capacity and weak penetration ability of brachytherapy, there is less impact on normal cells while still effectively killing tumor cells. After the radioactive particles are implanted inside the tumor, rays are continuously emitted to kill tumor cells for a certain period of time.

The results of this study showed that after 1 mo and 3 mo of treatment, the tumor lengths in the study group were lower than those in the control group, and the CR + PR rate of the study group was significantly higher than that of the control group, suggesting that TACE combined with ^{125}I implantation has a better anti-tumor effect than TACE alone and can significantly inhibit tumor growth [8-11]. The survival time of the patients in the study group was 22 mo, which was significantly longer than 18 mo in the control group. This result suggests that TACE combined with ^{125}I implantation can prolong the survival time of patients with PHC, and TACE and radionuclide therapy are an effective combination.

AFP is a broad-spectrum tumor marker with high sensitivity and specificity in monitoring disease changes and diagnosing PHC[1,2,10,22]. This study found that the serum AFP in the study group was lower than that in the control group after 1 mo and 3 mo of treatment, indicating that TACE combined with ^{125}I implantation can reduce the level of AFP. This likely occurred due to the ability of ^{125}I particles to ionize water molecules and cause direct damage to DNA. This affects the DNA repair mechanisms and can reduce AFP levels.

The CT perfusion imaging technique can effectively evaluate the hemodynamic changes of hepatocellular carcinoma tumors. This provides feedback on the micro-angiogenesis of tumor tissues and the surrounding tissues, which will direct the treatment of the cancer[12,16,23]. This study showed that after 3 mo of treatment the BV, PS, BF, HAF, and MTT measurements in the study group were lower than those in the control group, indicating that TACE combined with ^{125}I implantation can effectively reduce

Table 1 Comparison of changes in tumor lengths in the two groups of patients

Group	*n*	Before treatment	After 1 mo of treatment	After 3 mo of treatment
Study group	49	6.31 ± 2.00	4.11 ± 1.42	2.20 ± 1.04
Control group	49	6.14 ± 1.89	4.78 ± 1.50	2.81 ± 0.95
t value		0.432	-2.271	-3.031
P value		0.666	0.025	0.003

Data are presented as mean ± SD, in cm. Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation.

Table 2 Comparison of serum alpha-fetoprotein levels in the two groups of patients

Group	*n*	Before treatment	After 1 mo of treatment	After 3 mo of treatment
Study group	49	549.8 ± 130.7	342.0 ± 96.5	184.3 ± 67.8
Control group	49	530.6 ± 148.0	388.5 ± 86.0	219.5 ± 73.0
t value		0.681	-2.518	-2.473
P value		0.498	0.013	0.015

Data are presented as mean ± SD, in μg/L. Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation.

Table 3 Comparison of treatment efficacy in the two groups

Group	*n*	CR	PR	SD	PD	CR + PR
Study group	49	15	29	3	0	46 (93.88)
Control group	49	9	29	11	0	38 (77.55)
χ^2 value						5.333
P value						0.021

Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation. CR: Complete remission; PD: Progressive disease; PR: Partial remission; SD: Stable disease.

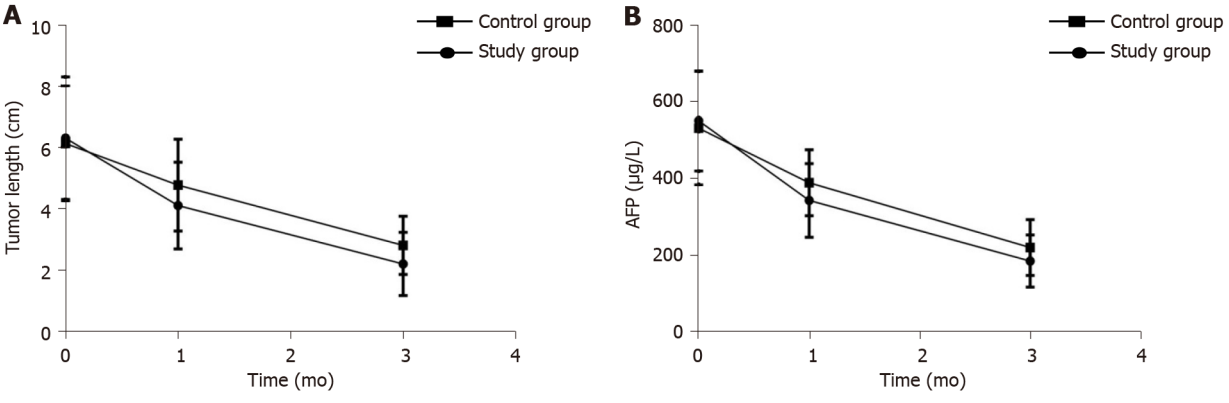

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Figure 1 Study group compared to the control group. A: Tumor lengths decreased in the study group compared to the control group; B: Serum alpha-fetoprotein levels decreased in the study group compared to the control group. Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation. AFP: Alpha-fetoprotein.

Table 4 Comparison of computed tomography perfusion parameters of the lesions in the two groups of patients

Perfusion parameters	Study group, *n* = 49	Control group, *n* = 49	*Z* value	*P* value
BV, mL/(100 g/min)				
Before treatment	23.16 ± 3.29	22.57 ± 4.02	0.795	0.429
After 3 mo of treatment	8.40 ± 2.20	10.01 ± 2.54	-3.354	0.001
PS, mL/(100 g/min)				
Before treatment	27.17 ± 5.48	26.20 ± 5.81	0.850	0.397
After 3 mo of treatment	12.64 ± 2.60	14.20 ± 3.13	-2.684	0.009
BF, mL/(100 g/min)				
Before treatment	254.8 ± 58.1	247.6 ± 63.4	0.586	0.559
After 3 mo of treatment	83.0 ± 24.7	100.2 ± 32.5	-2.949	0.004
HAF, %				
Before treatment	0.67 ± 0.17	0.64 ± 0.17	0.873	0.385
After 3 mo of treatment	0.24 ± 0.08	0.31 ± 0.10	-3.826	0.000
MTT, s				
Before treatment	7.60 ± 1.63	7.80 ± 1.55	-0.622	0.535
After 3 mo of treatment	5.20 ± 0.81	5.83 ± 0.96	-3.511	0.001

Data are presented as mean ± SD. Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation. BF: Blood flow; BV: Blood volume; HAF: Hepatic artery flow; MTT: Mean transit time; PS: Permeability surface.

Table 5 Comparison of survival rates between the two groups

Group	*n*	1 yr	2 yr	3 yr
Study group	49	46 (93.88)	34 (69.39)	21 (42.86)
Control group	49	44 (89.8)	30 (61.22)	13 (26.53)
χ^2 value		0.544	0.721	2.882
P value		0.461	0.396	0.090

Data are presented as *n* (%). Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation.

perfusion levels of tumor lesions, which improves clinical efficacy. ^{125}I particles implanted into tumor tissue release low-energy γ-rays, which exert direct killing effects, induce an inflammatory response, promote antigen-presenting cells such as macrophages to process and take up antigenic information, and promote B cells and T cells to participate in the tumor immune process[9,11]. In addition, the mammalian target of rapamycin pathway may form radiotherapy-specific proteins after several hours of irradiation. This activates lymphocytes, and the cytokine network regulatory mechanism is stimulated through the secretion of large amounts of cytokines, which activates tumor-specific immune processes to kill tumor cells. Related studies suggested that lower doses of γ-rays are more beneficial because they increase the responsiveness of lymphocytes, promote the production of antibodies, enhance the toxic effect on tumor cells, and improve the treatment effect[8,12].

CONCLUSION

This study confirmed that TACE combined with ^{125}I implantation for the treatment of patients with advanced PHC could better inhibit the formation of blood vessels in tumor tissues and reduce the perfusion level of tumor lesions compared to TACE alone. Therefore, with the development of technology, the combined multidisciplinary treatment improves the anti-tumor effect and plays a synergistic role in prolonging the survival time of patients, which is worthy of further clinical research.

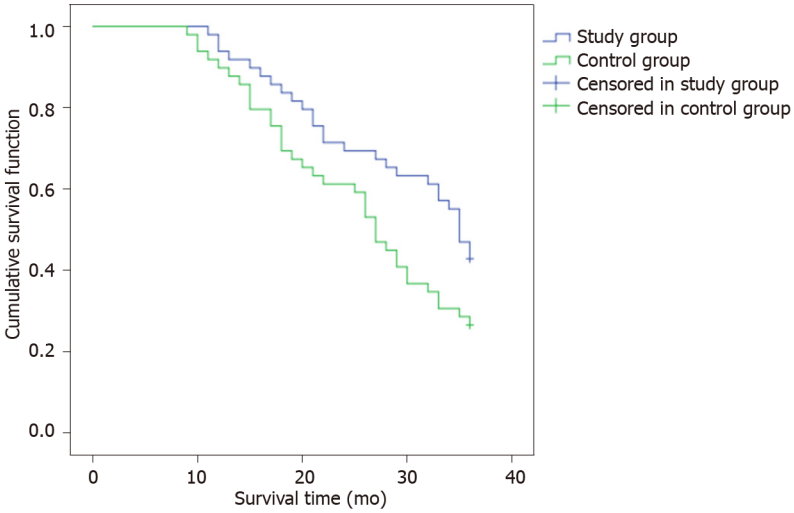

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Figure 2 Kaplan-Meier survival curvefor the two groups of patients. Control group: Treated with transarterial chemoembolization (TACE); Study group: Treated with TACE and radioactive iodine implantation.

ARTICLE HIGHLIGHTS

Research background

Primary hepatocellular carcinoma (PHC) is a malignant tumor with a high incidence in the Chinese population. Transarterial chemoembolization (TACE) is an effective treatment for PHC. Radioactive iodine (^{125}I) therapy has been used in the treatment of advanced PHC, especially in patients with portal vein tumor thrombosis.

Research motivation

Due to insidious onset and atypical early symptoms of PHC, more than 80% of hepatocellular carcinoma patients are diagnosed with metastasis and are ineligible for surgical treatment. Therefore, it is crucial to develop effective treatment methods, such as TACE and ^{125}I therapy. However, the data on the therapeutic effect of TACE combined with ^{125}I therapy in PHC is scarce.

Research objectives

To investigate the short-term efficacy of TACE combined with ^{125}I in patients with PHC.

Research methods

Ninety-eight patients with PHC were recruited and randomly divided into the study group (n = 49, treatment with TACE and ^{125}I therapy) and the control group (n = 49, treatment with TACE alone). The tumor length, alpha-fetoprotein (AFP) level, and computed tomography (CT) perfusion were recorded. Complete remission, partial remission (PR), stable disease and progressive disease were evaluated for all patients. Then, the efficacy was compared between the control group and the study group.

Research results

The tumor length and serum AFP level were lower in the study group compared to those in the control group after 1 mo and 3 mo of therapy. After 3 mo of treatment, the complete and PR rate in the study group was higher than in the control group (93.88% *vs* 77.55%, $P < 0.05$). Furthermore, CT perfusion parameters, including blood volume, permeability surface, blood flow, hepatic artery flow, and mean transit time, were all lower in the study group than in the control group ($P < 0.05$). The survival time of patients in the study group was 22 mo, which was significantly longer than 18 mo in the control group [log rank (Mantel-Cox) = 4.318, $P = 0.038$].

Research conclusions

For advanced PHC patients, TACE combined with ^{125}I implantation better inhibits the formation of blood vessels in tumor tissues and further reduces the perfusion level of tumor lesions compared to TACE alone. The combination of TACE and ^{125}I therapy improves clinical efficacy and plays a synergistic role in prolonging the survival time of patients.

Research perspectives

TACE combined with ^{125}I implantation or other therapeutic methods, such as radiofrequency ablation, programmed cell death ligand 1 therapy, and immune therapy, should be investigated in advanced PHC patients in the future.

FOOTNOTES

Author contributions: Dong J, Liu FQ and Wang L designed the report; Zhang Y, Wu YF, Yue ZD, Fan ZH, Huang K and Li YW collected the clinical data; Wang L, Huang K, Li YW and Zhang Y analyzed the data and wrote the paper; Huang K, Li YW, Dong J and Liu FQ performed quality control; Liu FQ contributed to administrative and financial support; and all authors read and approved the final version of the manuscript.

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Institutional review board statement: This study was approved by the Ethics Committee of the Beijing Shijitan Hospital, Capital Medical University, No. 201801.

Clinical trial registration statement: This study is registered at ClinicalTrials.gov, registration number ChiCTR-DDC-16009986 (www.chictr.org.cn/edit.aspx?pid=16996&htm=4).

Informed consent statement: Written informed consent was obtained from each patient.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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CASE REPORT

Intestinal erosion caused by meshoma displacement: A case report

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Abstract

BACKGROUND

A meshoma formation and erosion to the small intestine is rare. Herein, we report one case of a meshoma that was not treated early; causing it to displace and erode the small intestine, with infection, complete control of symptoms was achieved after removal of the infected patch mass, no recurrence of hernia after 2 years of follow-up.

CASE SUMMARY

A 62-year-old male patient presented with recurrent abdominal pain repeatedly for 1 wk, which has worsened 2 d before admition, accompanied by fever. Five years before presentation he underwent right inguinal hernia Plug and patch repair approach. Two years ago, a computed tomography scan revealed a right lower abdominal mass with soft tissue density, measuring approximately 30 mm × 17 mm, which was diagnosed as meshoma that was not treated. The patient had poorly controlled diabetes in the past year.

CONCLUSION

The formation of meshoma is rare, and that if not treated in time it might erode and require resection of the involved organ.

Key Words: Tension-Free mesh repair; Polypropylene mesh; Meshoma; Mesh infection; Bowel resection; Case report

Core Tip: The formation of meshoma increases the risk of infection. According to the literature, keep the surgical field clean when placing the mesh, pay attention to the flatness of the mesh, avoid curling and folding, and avoid any direct contact with the viscera. After the formation of the meshoma, surgery to remove the meshoma as early as possible is recommended.

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INTRODUCTION

Tension-free repair with mesh has become a standard surgical modality in adult inguinal hernia repair [1,2], significantly reducing the recurrence rate after inguinal hernia repair. As the use of polypropylene mesh in tension-free hernia repair has become more widespread, the clinical problems associated with it have also received increasing attention. At present, it has been proved that the foreign body reaction caused by implanted prosthetic materials can cause a series of complications, such as mesh displacement, adhesion and erosion, meshoma, chronic pain and even mesh infection.

Most mesh infections are acute, which usually occur during postoperative hospitalization or within 1-2 wk of discharge. The infection is mainly superficial and rarely involves the mesh. If not treated promptly, it can develop into a chronic mesh infection, which often ends up involving the mesh, forming a chronic infected sinus tract and causing delayed wound healing. Clinical manifestations of mesh infection include fever, painful local swelling, scleroma, erythema and even purulent discharge and fistula formation with the skin, the rate of mesh infection in open hernia repair is higher than that in laparoscopic hernia repair[3].

Conservative treatment including intravenous antibiotics, percutaneous puncture drainage or negative pressure suction to the wound has a high failure rate as the mesh is already infected and persists as a foreign body deep as a source of infection[4,5]. If the wound is not healed after repeated debridement and dressing change, the infected mesh should be removed as soon as possible[6]. It is still the most commonly used method to treat infection in clinic practice.

CASE PRESENTATION

Chief complaints

A 62-year-old male patient was admitted to the hospital with right lower abdominal pain for 1 wk, which has worsened in the last 2 d.

History of present illness

The patient's diabetes found in the past year and poor control of blood glucose level.

History of past illness

He had a history of multiple inguinal hernia repairs and had undergone a non-mesh repair of a left inguinal hernia at the age of 40 years. At the age of 57, he was diagnosed with a right inguinal hernia and underwent a plug and patch approach. At the age of 60, he underwent a transabdominal preperitoneal patch procedure for a recurrent left inguinal hernia.

Personal and family history

The patient had no family history of inguinal hernia disease.

Physical examination

Temperature 38.2 °C, heart rate 118 bpm, a hard mass was palpated in the right lower abdomen, about 4 cm × 3 cm in extent, poorly defined, with localized skin pressure and rebound pain, no myalgias, bowel sounds 4 bpm.

Laboratory examinations

Complete blood count: White blood count (WBC) 12.5, reference 3.5-9.5 with units of 10^9/L; neutrophils 11.4, reference 1.8-6.3 with units of 10^9/L; C-reactive protein (CRP) 146.56, reference 0-8 with units of mg/L; fecal occult blood test (+); fasting blood sugar 14.73, reference 3.89-6.11 with units of mmol/L;

hemoglobin A1c 12.2%, reference 3.6-6.5.

Imaging examinations

A computed tomography (CT) scan 2 years ago revealed a sigmoid herniation into the left scrotum and a right lower abdominal mass with soft tissue density, measuring approximately 30 mm × 17 mm, with a clear surrounding fatty space. This preoperative contrast-enhanced CT scan of abdomen: a mass soft tissue density shadow with a size of about 32 mm × 26 mm can be seen in the lower right abdomen, with lower density in the center of the lesion, poorly defined borders and blurred surrounding fatty spaces, with enhanced edges and no enhancement in the central region (Figure 1).

FINAL DIAGNOSIS

Mesh infection, meshoma, gastrointestinal bleeding, and type 2 diabetes.

TREATMENT

Comparing abdominal CT in 2018 and 2020, it was found that the right lower abdominal mass was not significantly enlarged, the center of the mass was not enhanced, and the surrounding fatty spaces were blurred. Combined with the patient's diabetes found in the past year and poor control of blood sugar level, the right inguinal hernia was treated with mesh plug plain patch 5 years ago. This right lower abdominal mass was initially considered as meshoma with infection. After intravenous antibiotic treatment for about 10 d before operation, the patient's body temperature, WBC and CRP were normal, and the blood sugar levels were well controlled after standardized hypoglycemic treatment (Figure 2), but the mass did not shrink. It was discussed and the decision was made to perform a laparoscopic exploration. Intraoperatively, a portion of the right lower abdominal ileal canal was found to be congested and oedematous, with dense adhesions forming to the abdominal wall (Figure 3). The central texture was firm, and sharp dissection with scissors revealed a mesh-like structure with outflow of pus (Figure 3B). The mass was completely separated from the abdominal wall, but not from the small bowel, so it was converted to open surgery. It was found that the mesh had eroded the ileal canal, so part of the ileum was resected along with the mass. Postoperative autopsy revealed a central mesh structure and a cavity in the mass (Figure 3E).

OUTCOME AND FOLLOW-UP

Gastrointestinal endoscopy 1 mo after surgery did not reveal abnormal lesions. There was no recurrence of the inguinal hernia during the 2-year follow-up.

DISCUSSION

The incidence of mesh infections ranges from 0.11% to 5.00%[7,8] and 0.7%-2.0% after laparoscopic inguinal hernia repair and up to 6%-10% in open-mesh techniques[9]. Risk factors for mesh infection include the patient's underlying disease such as diabetes, coronary artery disease, chronic obstructive pulmonary disease, smoking, morbid obesity, malnutrition and immune deficiency[7,10]. But also, the type of mesh, the timing of the procedure, the surgical approach, whether the mesh was placed flat, the management of early postoperative complications such as haematoma or seroma requiring surgical management, the surgeon's experience, and the use of improperly sterilized instruments, *etc.* The most common pathogens are *Staphylococcus aureus* and *Staphylococcus epidermidis*, in addition to several anaerobic bacteria of the genus *Streptococcus* and *Enterobacteriaceae* that play a key role in the pathogenesis of hernia repair mesh infections[11,12]. The bacterial culture of this patient yielded *Streptococcus agalactiae* (Group B Streptococcus, group B strep, GBS), which is a Gram-positive conditional pathogenic bacterium that is commensal in the human intestine and vagina. It causes severe and potentially fatal infections mainly in neonates and the elderly, while carriers have no obvious symptoms [13], the drug sensitivity of this patient was sensitive to penicillin, moxifloxacin, vancomycin and tegacyclin, except for tetracycline and clindamycin.

When the patch becomes infected, bacteria attach to the surface of the mesh and can form a microenvironment called "biofilm"[3,4,14]. Through its three-dimensional structure, the biofilm provides mechanical stability for bacteria and physical protection against external stressors (immune cells and therapeutic compounds, including antibiotics), rendering any conservative therapeutic measures ineffective[4]. As a result, this infection is usually persistent, with poor response to antibiotics and often

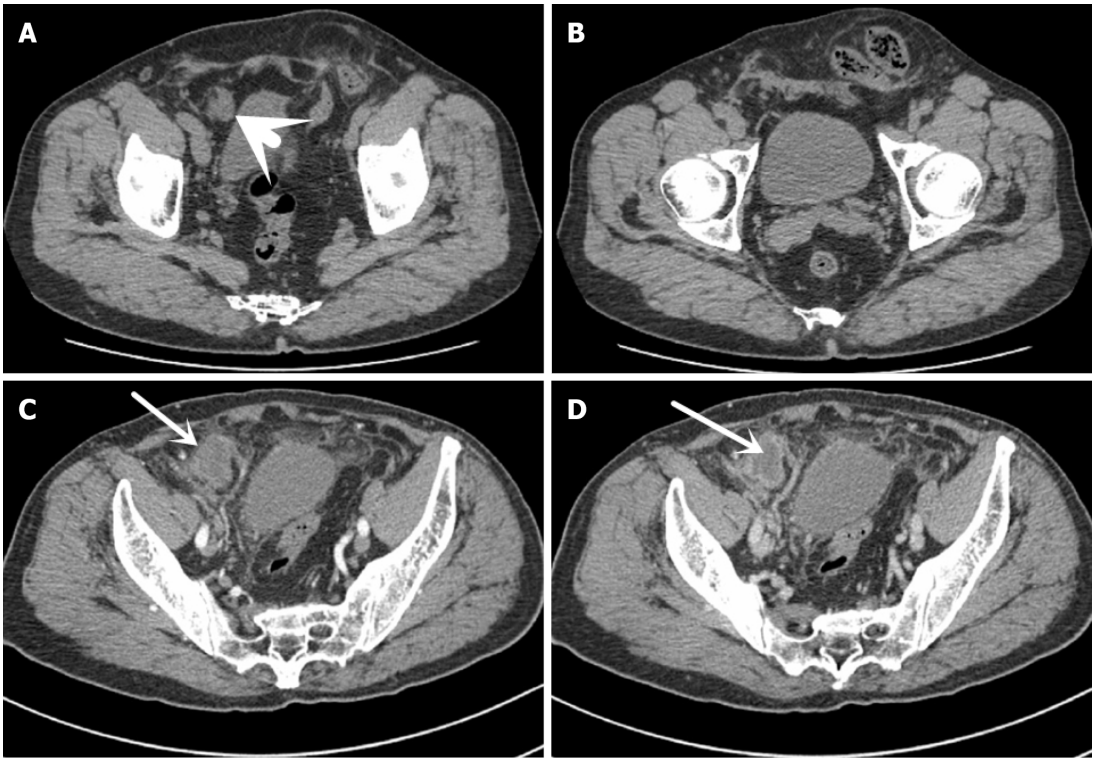

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Figure 1 Computed tomography. A: Abdominal computed tomography (CT) in 2018 reveals a left indirect inguinal hernia, and a hypodense focus (short arrow) in the right lower abdomen; B: The contents of the left indirect inguinal hernia are the sigmoid colon; C: Abdominal CT in 2020 shows a mass on the lateral side of the right umbilical artery (long arrow), with no obvious enhancement in the arterial phase; D: The central part of the mass is found to be more hypointense in the venous phase (long arrow), with circumferential enhancement around the edges of the mass.

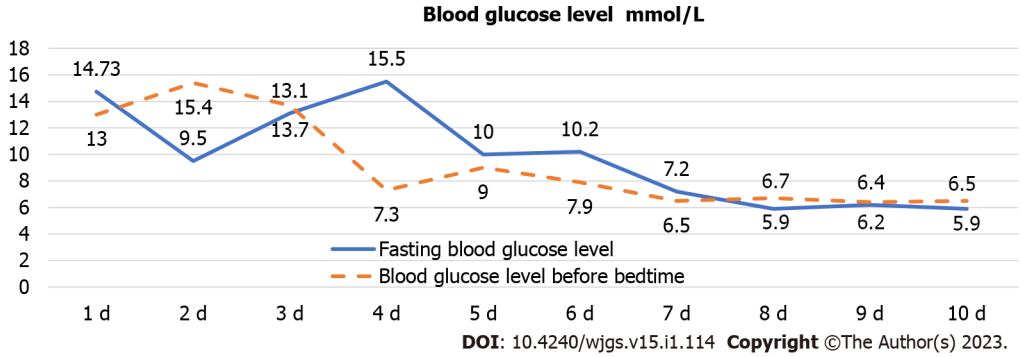

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Figure 2 Blood glucose control levels. Continuous fold is fasting, intermittent line is bedtime.

requiring surgical treatment. It has been suggested that removal of partial mesh is associated with a 50% incidence of persistent prosthetic infection and a significant increase in the incidence of surgical site occurrence and reoperation. In the case of clean contaminated wounds and mesh-associated infection or fistula, the previous mesh should be completely removed whenever safe and feasible[15]. Open debridement can be very extensive and complex, and complete resection is often not achieved, especially when internal organs, especially hollow organs such as the bladder, colon or small bowel, are heavily attached to the abdominal wall or eroded by the mesh[16]. In such cases, the laparoscopic technique demonstrates its advantages. This technique allows a thorough exploration of the abdominal cavity, locating the focus of infection, determining whether there are adhesions and whether internal organs are involved and guiding further treatment, thus allowing unnecessary destruction of the healthy layers of the abdominal wall and nearby organs to be avoided.

Mesh infections can lead to catastrophic consequences, severely affecting the lives of patients and increasing the cost of healthcare to society[17]. This makes preventing patch infections far better than treating them. According to the literature conclusion, the following suggestions are made for the placement of the patch[18,19]. Firstly, choose the right type of mesh. Although patches are widely used

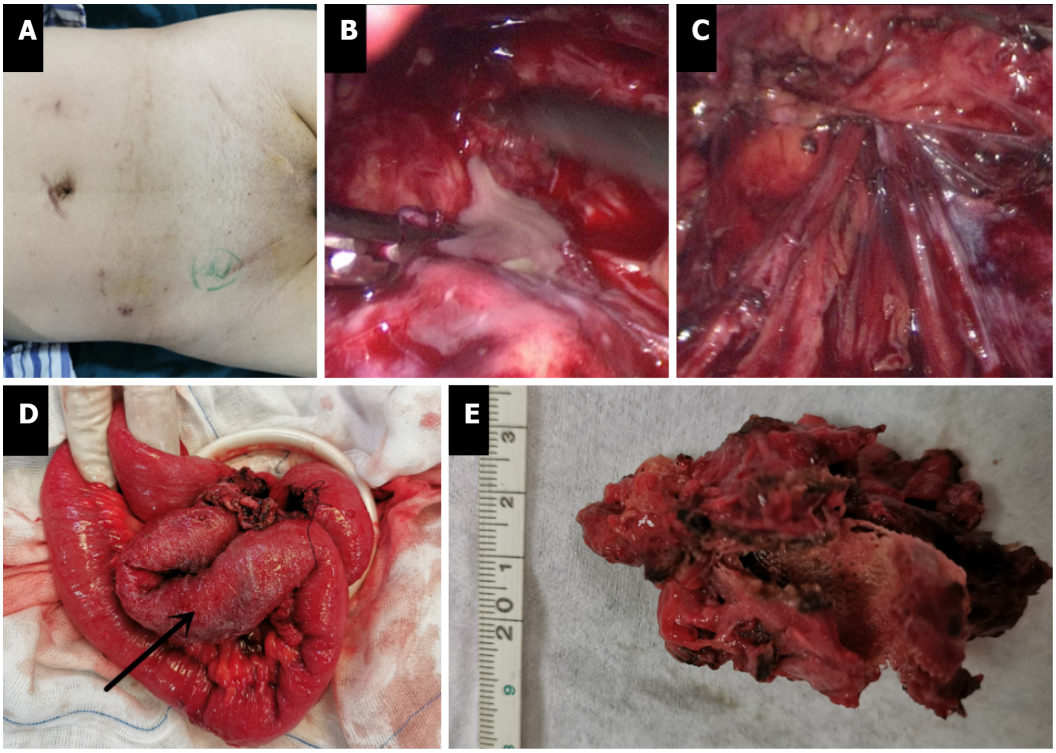

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Figure 3 Intraoperative findings. A: Surgical scar after multiple inguinal hernia repairs; B: Greyish white, purulent, viscous fluid from the mass found intraoperatively; C: Examination of the vas deferens and spermatic vessels after debridement of the mass with no damage and no defective weak areas in the internal ring opening or abdominal wall; D: Partial exfoliation of the ileal canal pulpy muscle layer (arrow) with tortuous intestinal ducts in a mass, closely related to the meshoma; E: Postoperative autopsy reveals a central non-resorbable mesh structure and a cavity in the mass.

in inguinal hernia repair, guidelines do not recommend the use of mesh plugs[1]. Mesh plugs are more likely to enter the abdominal cavity due to their conical shape and heavier weight, but are equally more likely to cause friction and even erosion of the organs. Among the various types of mesh, polypropylene is the preferred material because it is chemically inert, stable, non-immunogenic, non-toxic, flexible, and lightweight, has high tensile strength and is relatively resistant to infection. Secondly, attention needs to be paid to the details of the surgical procedure. It is necessary to keep the surgical field clean when placing the mesh, pay attention to the flatness of the mesh, avoid curling and folding, and avoid any direct contact with the viscera (vital), which can greatly reduce complications. When not fixed, inadequately fixed or inadequately dissected so that there is insufficient space for the mesh, this can lead to folding and curling of the mesh and eventually to the formation of a bulbous mass called a meshoma, a phenomenon first identified and named by Amid[20] in 2004. Thirdly, we must also not neglect the importance of surgical documentation. The size of the original hernia defect, the type of repair, the mesh material, the exact anatomical position of the mesh placement and the fixation technique must be accurately documented to provide as much information as possible for possible reoperation in the future. Finally, improving the patient's own physical state. For example, quitting smoking, controlling diabetes and reducing the patient's weight can greatly reduce the risk of wound complications[5].

CONCLUSION

The incidence of mesh infection is rare and, when it does occur, it has serious consequences for the patient and poses therapeutic difficulties for the surgeon, while treatment outcomes are often unsatisfactory. The formation of meshoma can not only cause mesh infection, but may even erode and require removal of the affected organ if left untreated. Therefore, after the formation of the meshoma, surgery to remove the meshoma as early as possible is recommended.

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